News&Features from NIH

January 1981

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L'Tot, a three-day old cynomolgus monkey clings to her mother. She is the first infant born as a result of low tubal ovum transfer. For more details on this story see page 4

A pair of glasses, a computer, and hard work pave the way for a paraplegic to communicate once again with the outside world. See page 00 for more details.

AML patients are currently given three common cancer drugs which seem to promote a longer remission period than previously tried drug combinations. This NCI sponsored program is in operation in several leading Cancer treatment centers throughout the country.

See page 4.

Scientists are discovering more evidence for an immune response in patients with multiple sclerosis. The response may be linked to the formation of lesions in the nervous system, that marks this disease.

See page 5.

Environmental toxins are everywhere. In laboratory animals many of these chemicals have been found to adversely affect the intestines. . . and may pose a threat to man as well.

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New Technique May Help Infertile Women Become Pregnant

By Jody Dove

Scientists at the National Institutes of Health have succeeded in enabling monkeys with blocked fallopian tubes to become pregnant through a technique they developed called low tubal ovum transfer. Offered as an alternative to *in vitro* (test tube) fertilization, this new procedure may have important implications for many infertile women.

When an egg is released by an ovary, it normally travels to one of the fallopian tubes where it can be fertilized by a sperm. If the fallopian tubes are blocked, however, conception cannot occur.

Blocked fallopian tubes are the most common cause of infertility in women. Surgery to repair the tubes is successful only about half the time. Low tubal ovum transfer has the potential of offering to these women with irreparably blocked tubes an opportunity to become pregnant if their tubes are functional near the uterus. Furthermore, fertilization would take place *in vivo* (inside the body), rather than in a test tube.

Drs. Gary D. Hodgen and Olivier Kreitmann, the two scientists from the Pregnancy Research Branch at the National Institute of Child Health and Human Development responsible for the development of the procedure, conducted their research on monkeys, because of the similarities in the menstrual cycles of women and monkeys.

To begin their research, the doctors first surgically blocked the fallopian tubes of 55 rhesus and cynomolgus monkeys near the ovary. After tracking the hormonal levels of the monkeys to determine when ovulation would occur, each monkey was mated the day before her egg was expected to be released.

Within 12 hours of the anticipated time of ovulation, the doctors made a small incision in the abdomen of each monkey and examined the ovary with a laparoscope to ensure that the preovulatory follicle, the sac on the ovary containing the egg, had not already ruptured. Fifteen of the monkeys had already ovulated, and therefore could not undergo low tubal ovum transfer. Using a hollow needle, the doctors extracted the contents of the follicle from the remaining 40 monkeys, who were just on the verge of ovulating.

The follicular contents were examined under a microscope to ensure that an egg had been aspirated. Thirty-one of the 40 monkeys had eggs successfully extracted from their ovaries. These eggs were then injected into the fallopian tubes of the monkeys between one and two centimeters from the uterus where their tubes were open, and the monkeys were mated again.

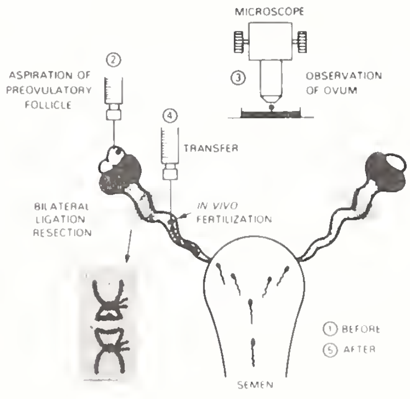
Of the 31 monkeys who had eggs inserted into their fallopian tubes, five became pregnant and delivered normal infants. This 16 percent success rate closely resembles that of normal fertilization in humans, in which a couple has a 15-20 percent chance of conceiving during each menstrual cycle.

The scientists from the NIH cautioned, however, that further animal research is needed before this technique can be tried in women. One of the risks involved could be the danger of ectopic pregnancy, in which the fertilized egg would develop in a fallopian tube, possibly leading to rupture of the tube.

Another problem requiring further refining is timing when the follicular contents should be extracted. If it is aspirated too soon, the egg will not be mature enough to combine with a sperm. If the egg has already been released, the procedure cannot continue. The new technique of ovarian ultrasonography may help in locating and determining the maturation of a follicle in the future.

A potential problem also exists if too many granulosa cells—cells unavoidably removed during aspiration of the follicle—are extracted along with the egg. These cells later form the corpus luteum, a structure on the ovary which secretes the hormones necessary to sustain a pregnancy. If too many granulosa cells are removed, a woman's hormonal level could become too low to support the fetus, although hormone therapy may improve the outcome in this situation.

LOW TUBAL OVUM TRANSFER



Low tubal ovum transfer avoids some ethical questions that have been raised concerning *in vitro* fertilization. "The need for someone to decide whether a given embryo is fit for transfer to the uterus or should be discarded is not encountered with low tubal ovum transfer," Dr. Hodgen explained.

In low tubal ovum transfer, only one egg is aspirated, and there is no concern about wasting unused eggs. Moreover, a better rate of pregnancy can be achieved than through *in vitro* fertilization, and the conditions of the maternal milieu whic encourages a fertilized egg to grow are better preserved than in a laboratory dish.

If additional animal model studies prove that low tubal ovum transfer is an effective and safe procedure, trial studies may be attempted in women. ■

New Drug Therapy Promises Longer Remissions for Many AML Patients

By Susan Gerhold

Acute myelogenous leukemia (AML), one of the most stubborn and incurable kinds of leukemia, is beginning to respond to new chemotherapy treatments.

In a study recently completed this summer, 70 percent of AML patients went into complete remission, that is the patient appears to have no signs or symptoms of th disease, after undergoing a 15-month ant leukemic therapy program. Researchers predicted that patients would remain in remission 12 to 24 months and evidence now shows that 29 AML patients studied under this research project have remained disease free after two to four years. Several other studies around the country are yielding similar results.

AML, a type of cancer that affects the blood and blood forming organs, strikes 20,000 people each year, primarily adults, but some children as well. Myelogenous leukemia affects the granulocytes or white blood cells that are produced in the bone marrow. Granulocytes normally engulf and digest bacteria and other small particles. The patient may first come down with a cold, and sometimes the lymph nodes, spleen and liver become enlarged. Bone pain, paleness and a tendency to bleed easily are also symptoms as well as the susceptibility to infections.

Until lately, remission rarely exceeded a year. Most patients who initially responded to treatment suffered a relapse or reappearance of signs and symptoms of the disease after being essentially well during remission.

The goal of current studies is to improve the duration of complete remission by attempting to prevent relapse. For i stance, researchers at the Sidney Farber Cancer Center in Boston planned a four-month period of intensive treatment to reduce leukemic cells in the hope that remission would last longer and relapse would not occur as quickly.

Under a research grant supported by the National Cancer Institute, 83 patients [illegible] AML were seen at various hospitals throughout the country from February 1976 to October 1979. The patients, all under 50 years of age, had not been previously treated for AML. Chemotherapy was given in two phases: a remission-induction phase and an intensive sequential combination phase.

A treatment regimen consisting of vincristine, doxorubicin, prednisolone, and cytarabine—commonly used cancer drugs—was administered. Two weeks after this treatment, a bone marrow and biopsy were performed to detect the presence of leukemic cells. If the patient showed no signs of the disease, then the second treatment was started.

At the end of the first stage, 58 patients out of 83 went into complete remission. Of these, 40 went into remission after one course of therapy; whereas the rest required two courses of therapy.

At the second stage, the program was divided into four drug sequences which took 14 months to administer. Those patients who showed continuous complete remission stopped therapy after sequence IV or approximately 15 months after beginning the research project.

As with all cancer drugs, some side effects were noted. All patients temporarily [illegible] their hair and many experienced vomiting and nausea. Several did not survive the rigorous 15-month program and five elected to withdraw completely.

Currently, 22 patients have completed the program and only four have relapsed. According to Dr. Peter Wiernik, Acting Associate Director for NIH's Baltimore Cancer Research Center, "Seven out of 10 AML patients are responding quickly to treatment today. In the past, most soon relapsed. Now about 25 percent of responders are running at least 4 to 5 years disease-free."

"The important thing," said Dr. Howard Weinstein of the Sidney Farber Cancer Research Institute, a participating cancer center, "is to tell people there is a reasonable chance today for long survival and that patients should be referred to major cancer centers for evaluation and treatment."

The only other therapies that appear to induce remission in AML patients are intensive chemotherapy and total-body irradiation followed by a bone marrow transplantation—rigorous procedures that many cannot undergo.

Many researchers are also perfecting the use of antibiotic therapy to prevent bacterial infection, the most common cause of death in acute leukemia patients.

The study on which this material is based was published in the *New England Journal of Medicine*, August 28, 1980, Vol. 303, No. 9, p. 474. ■

Flow Cytometry Detects Immune Response in MS Patients

By Helen Ou

Neurologists at the University of Chicago have discovered that lymphocytes, a type of white blood cell, proliferate in the cerebrospinal fluid (CSF) of patients with multiple sclerosis (MS) when the disease is active. This is the first demonstration that white blood cells of MS patients are actively dividing in cerebrospinal fluid (CSF). The presence of these proliferating lymphocytes reflects an immune response in MS patients.

An estimated 125,000 Americans are afflicted with MS, with young adults between the ages of 20 to 40 being the most susceptible. It is a disease of the central nervous system which is characterized by the destruction of patchy myelin (demyelination) which surrounds axons in a seemingly random manner. Often symptoms, which may involve the impairment of sensory and motor functions of the body, occur and disappear (or lessen) in a varying and unpredictable fashion. Other patients may experience a gradual and progressive deterioration of function. Thus, patients may have active (rapid or clearly perceptible worsening of symptoms), progressive (gradual increase of symptoms), or stable (no new symptoms or worsening for six or more months) multiple sclerosis.

The research by Drs. Avertano B. C. Noronha, David P. Richman and Barry G.W. Arnason at the University of Chicago used a new technique, flow cytometry, that permits rapid assessment of the cells in the cerebrospinal fluid. Cells are treated with a fluorescent stain. When subjected to a laser beam, the DNA in these cells glows green and the RNA in the cells glows red. Cells about to divide first produce additional RNA. The amount of RNA present in the cells is an indication of cell division. These findings are automatically recorded and stored in a computer memory.

Noronha and his group studied 21 specimens of CSF from 17 MS patients. Three patients were studied on more than one occasion. Sixteen age-matched hospitalized patients who were undergoing lumbar puncture for other conditions were studied and used for comparison.

These scientists found that cells from patients in an active stage of MS contained the highest RNA levels. Cells in the progressive and stable stages contained less RNA and cells from non-MS patients

Dr. Noronha places stained cerebrospinal fluid cells from MS patients into cytofluorograf machine to be analyzed by the flow cytometric technique.

NIH PHOTO #1653

Drs. Barry G. W. Arnason (left), Avertano B. C. Noronha, and David P. Richmond (right) at the University of Chicago, Department of Neurology, study the cell-cycle phase of lymphocytes from cerebrospinal fluid with the sophisticated technological equipment available at the Brain Research Institute. NIH PHOTO #1654

Kathy Astroth at the University of Chicago, Department of Neurology, points to the laser beam in the cytofluorograf machine modified with an argon-ion laser. Cells to be analyzed pass through the laser beam glow green for DNA content and red for RNA content. NIH PHOTO #1655

contained the least amounts. The data suggest that there is a population of lymphocytes in the spinal fluid of MS patients that proliferates, probably, in response to some antigen. Noronha says, "What is most interesting is that during acute attacks of MS, these lymphocytes move right through the cell-cycle. During an acute attack, there is a greater turn-on."

Previous studies have demonstrated that in active MS patients, the suppressor cells, a type of white blood cell, are low in the peripheral blood. However, since the MS disease process is in the central nervous system, the brain and spinal cord, it is more important to know what is going on in the CSF, which bathes them.

The flow cytometry study adds to evidence that the body's own so-called immune mechanism, which acts through white blood cells, is involved in MS. "Whatever the mechanism of lesion formation may be, it appears established that immune responses occur in the central nervous system in MS," says Noronha.

According to Noronha there have been reports of increased numbers of lymphocytes in CSF in MS patients, but previous methods were painstaking and required that the cells be cultured. "The beauty of this method (flow cytometry) is that it doesn't require too many cells and you can do it with a minimum of time," says Noronha. "You can do it right away after you take the living cells out of the patient. In CSF, the number of cells is very few, normally, and it is difficult using other methods to make accurate measurements."

This study was supported in part by a grant from the National Institute of Neurological and Communicative Disorders and Stroke, and was reported in the September 25, 1980 issue of *The New England Journal of Medicine.* ■

Hot Flashes Are Not "Just in the Mind" —They're in the Brain

By Jerry Gordon

Research supported by NIH's Division of Research Resources, indicates that hot flashes experienced by postmenopausal women are caused by biochemical events in the brain.

Gynecologists Howard L. Judd and David R. Meldrum of the UCLA School of Medicine say that the brain suddenly shifts the body's temperature during these episodes. The sudden warmth of a hot flash is the brain's first perception of this shift, and the subsequent symptoms of perspiration and flushing are automatic cooling mechanisms.

The advent of estrogen therapy in the 1930's and 1940's solved these discomforting problems for many postmenopausal women, but it was later found that estrogen therapy increased the risks of breast and uterine cancer. Currently, researchers are looking for alternate treatments which might avoid these risks.

Changes in blood hormone levels d ing hot flashes seem to originate in the hypothalamus, the area of the brain which controls the production of certain hormones by the pituitary and controls many basic drives, such as appetite, sexuality and responses to temperature.

The UCLA researchers at the General Clinical Research Center found that 94 percent of hot flashes are associated with sudden releases of luteinizing hormone (LH) from the anterior pituitary lobe of the gland into the blood. This suggests that LH or, more likely, the factors that cause LH release may be related to, or may directly trigger a hot flash.

The UCLA researchers studied five postmenopausal women who suffer from frequent hot flashes. Using a thermistor applied to the finger, they recorded the skin temperature as an index of flushing and measured body perspiration using the galvanic skin response. The disturbances occurred throughout the day and night, without any evident circadian rhythm. Flushing and perspiration were surprisingly uniform. For example, one woman noticed within 45 seconds that she was experiencing a hot flash and at the same time her skin conductance rose sharply. Forty-five seconds later, the temperature of her finger began rising and attained average increase of 4°C within ni minutes.

These studies suggest that a central thermoregulatory adjustment is made in the brain. Events such as the increased conductance of the skin and elevation of temperature in the finger are controlled by neurotransmitters (SNS), such as acetylcholine and norepinephrine, of the sympathetic nervous system.

Additional tests monitored temperature on the tympanic membrane of the ear, the best noninvasive technique for measuring the temperature of blood flowing through the hypothalamus or the core temperature. Researchers found that the core temperature starts falling about 4 minutes after a hot flash and reaches the lowest point (0.2)° in about 18 minutes.

Investigators believe that changes in core temperature reflect the brain's action to regulate body temperature. The hypothalamus monitors the core temperature and compares it to a temperature set in the hypothalamus. This set point, the core temperature and prevailing temperature all interact together and regulate the body's temperature.

To explain the mechanism of a hot flash, Dr. Judd reasons that the hot flash could result from a sudden drop in the set point, which can be changed by a variety of agents.

One agent is a pyrogen, an agent that causes fever. The set point suddenly rises, and the hypothalamus recognizes that its normal core temperature is too low, and the patient feels cold. If the set point is suddenly lowered, the core temperature is [illegible] high, and the person feels hot, then a hot flash occurs.

A woman experiencing a hot flash may try to cool off by fanning herself, thinking cool thoughts, or by relaxing. The brain at the same time, also acts via the sympathetic nervous system to bring the body's temperature down to the set point.

In an attempt to explain how the drop in the set point is triggered, Dr. Judd speculates that it might result from an abnormally large release of luteinizing hormone releasing hormone (LHRH) or from a sudden release of an agent (like the pyrogen) which causes the release of LHRH.

Some of the LHRH neurons are located close to the temperature regulating nucleus in the hypothalamus, and researchers propose that an abnormally large release of LHRH or factors responsible for their release, may spread to the temperature-regulating nucleus, causing a sudden drop in set point. However, on the other hand, the sudden release of a neurotransmitter which influences both LHRH and the temperature set point might simultaneously cause both the large release of LHRH and a drop in the set point, according to Dr. Judd.

There are approximately 30 million postmenopausal women in the United States, many suffering from hot flashes. Besides the discomfort of these episodes, hot flashes may sometimes lead to chronic sleep disturbances. UCLA physicians are currently testing agents which are less risky than estrogen therapy. Compounds called alpha-adrenergic antagonists that inhibit neurotransmitters or norepinephrine activity in the brain have been shown to successfully block the release of LH in primates. Presumably, they antagonize the stimulation of LHRH release. Progestins also suppress LH by acting on the hypothalamus and may provide a safer alternative to estrogen for some women. Researchers are now conducting clinical trials on these drugs to determine if they prevent hot flashes.

This research was supported by the University of California at Los Angeles and the General Clinical Research Centers Program of the Division of Research Resources, NIH. For further information, write to Dr. Howard L. Judd, Center for Health Sciences, School of Medicine, Room 22-177, University of California, Los Angeles, California 90024. ■

NIH Consensus: Cesarean Births Do Not Always Have to Be Repeated

By Jody Dove

"Once a cesarean, always a cesarean," is a practice no longer irrefutable, according to a panel of experts at a recent Consensus Development Conference on Cesarean Childbirth held at the National Institutes of Health, September 22-24. The panel arrived at this consensus after considering three days of evidence on the medical, psychological, economic, ethical, and legal factors involved in the recent rise in cesarean deliveries.

During the past decade, the cesarean birth rate has tripled, from five percent of all deliveries to 15 percent. Many physicians believe that during complicated labors, cesarean births improve the outcome for both mothers and babies. However, concern about the frequency of this procedure has led to a reconsideration of when cesarean births are necessary.

The consensus statement reflects the judgment that this trend of rising cesarean rates may be stopped or reversed, without impeding progress toward reducing maternal and infant mortality and morbidity.

A large proportion of the rising cesarean rate is attributable to repeat cesarean births. Most women who deliver the first time by cesarean birth undergo the procedure in subsequent deliveries. The reason for repeat cesareans has been the fear that the scar layers from the previous incision would separate and the uterus rupture during normal labor.

The panel recommended that this policy of repeat cesareans be revised because more than 90 percent of all women who have a cesarean birth now have a low horizontal incision—also called a low transverse incision—which is not as susceptible to rupture as the classical vertical scar.

The panel issued guidelines under which a woman with a low transverse scar can attempt labor. If a woman can get to a hospital equipped to handle an emergency cesarean birth within fifteen minutes or less, if adequate anesthesia services are available, if adequate nursing and obstetrical staff are present in the operating room, and if adequate blood for transfusions is available, then it may be safe to attempt a vaginal delivery.

The panel also examined the need for cesarean births in deliveries complicated by dystocia. Dystocia, a catch-all category for abnormal labor due to inadequate progress in labor or to problems caused by the size and position of the fetus, accounts for 30 percent of all cesarean births.

When a woman is not progressing normally in labor, the panel suggested that other means may be employed to stimulate labor before resorting to a cesarean birth. These methods include rest, walking, sedation or starting an IV for hydration. In some cases, the use of oxytocin—a drug which stimulates uterine contractions—may have favorable results.

Malpresentations of the fetus, in which the fetus is not turned in the normal headfirst position, requires analysis on an individual basis to determine the best outcome for mother and infant, said the panel.

The size of the infant also plays an important role in determining the safest method of delivery. While unusually small or large babies require special care, it is possible that cesarean births can be reduced for babies of normal weight. The panel concluded that peer review within hospitals may help in setting up guidelines for handling dystocia cases.

Breech presentations also pose problems in determining the proper type of delivery. Between 1970 and 1978 the rate of breech infants delivered through cesarean births increased from 11 percent to 60 percent. Although traditionally, obstetricians delivered breech babies vaginally, in recent years cesarean births have been the preferred method. The panel recommended that if the fetus weighs less than 8 pounds, if the mother's pelvis is large enough, and if the physician experienced in handling breech delivery is in attendance, vaginal delivery may be an appropriate choice.

Diagnoses of fetal distress due to the increased use of fetal monitoring have also increased the number of cesarean births. In the event of fetal distress, assessment of possible trauma to the fetus must be made in choosing the delivery route.

Other recommendations of the panel include liberalizing hospital policies to include the father or partner to attend the cesarean birth, to avoid the unnecessary separation of healthy newborns from their parents after a cesarean birth, to allow women to decide on regional rather than general anesthesia and to improve methods of assessing fetal maturity.

The panel urged obstetricians to obtain the informed consent of parents before performing a cesarean delivery, especially in non-life-threatening instances. Further research, and more data on morbidity and mortality rates concerning mothers and infants, are needed on this controversial subject so that doctors and parents can make appropriate choices in choosing the safest delivery.

The NIH Consensus Development Conference was sponsored by the National Institute of Child Health and Human Development, in conjunction with the National Center for Health Care Technology, and with the assistance of the Office for Medical Applications of Research. ■

Environmental Toxins Adversely Affect Intestines of Lab Animals

By Susan Gerhold

Newspapers fill their pages with stories of another oil spill, a chemical disaster, a fatal food poisoning, or another ecological calamity. Our air is often full of pollutants such as dust, fumes, dirt, or chemicals. And sometimes we are just innocent victims of chemical and environmental exposure, such as the toxic spill in Seveso, Italy, or the PCB exposure in Yusho, Japan.

Environmental disasters have unfortunately became a serious and sometimes frequent occurrence in our lives. So it was appropriate for the NIH Nutrition Coordinating Committee (NCC) meeting to have Dr. Carol Schiller, a leading toxicologist, talk about environmental toxins and their effects on laboratory animals. The committee meets once a month to discuss research on nutrition and reviews studies on such subjects as infant feeding, the relationship between diet and cancer, diet and cardiovascular disease, levels of obesity, and the role of nutrition in aging.

Dr. Schiller is in charge of the Gastrointestinal Function and Toxicology Work Group (GIFT), a part of the Laboratory of Organ Function and Toxicology, within the National Institute of Environmental Health Sciences (NIEHS). Dr. Schiller presented her recent findings on chemical exposure by focusing on toxic effects in the intestines of test animals.

The intestine is an important organ for digesting and absorbing nutrients. Some of the intestines' major functions are to act as a transfer agent in allowing certain nutrients to be absorbed into the blood and to promote the passage of nonabsorbed wastes out of the body.

The GIFT researchers decided to look more closely at both overt and subtle toxic effects, especially those that result from environmental contamination or from exposure on the job. A brief description of various toxins that the GIFT researchers studied recently are explained here.

In one study, 1,2 dimethylhydrazine (DMH), a synthetic chemical similar to a component of jet fuel, was found to cause colon cancer, after a single dose, in 80 percent of the exposed animals. Since colon cancer is found in older adults, the researchers waited nearly two years after exposure to study the effects on these test animals, making them more comparable to elderly adults.

In another DMH study, pregnant rats were given a single dose of the agent, which was later found to change enz[illegible] activity in their intestines. Previous reports had cited evidence that tumors developed in the brain and jejunum (a part of the intestine) of the offspring after prenatal exposure to the chemical.

The effects of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD), a by-product of the herbicide in Agent Orange (used as a defoliant in Vietnam, exposing many American soldiers as they walked through the brush), were also observed. A special strain of adult female rats was exposed to TCDD at 10 weeks of age. One group was given TCDD in corn oil after fasting 16 hours and the control group was given corn oil only. After feeding, both groups of animals were sacrificed and then examined.

A pregnant rat's milk is drawn after being fed acrylamide. The animal's milk is drawn manually into a calibrated capillary tube for chemical and radiochemical testing. NIH PHOTO #1656

Results showed that in the exposed animals the less differentiated intestinal crypt cells were more susceptible and sensitive to enzyme induction than the more differentiated absorptive tip cells. This was the first demonstration that normal undifferentiated, proliferating cells responded to chemical exposure such as TCDD.

Another environmental agent, acrylamide, a residue sometimes found in plastic, is a known poison to the nervous system. This agent was given to pregnant rats within the 6th and 17th day of gestation for 10 successive days. One study showed that the offspring had high levels of acrylamide in their bodies, which they received through the placenta. Another study showed that the development o[illegible] zymes in the intestines of the treated offspring was changed compared to that of the unexposed offspring.

Polychlorinated biphenyls (PCBs) found in electrical transformers, were another environmental toxin studied recently by the GIFT researchers. Pregnant rats were fed several biphenyls orally on days 8, 11, 13, 15 and 18 of gestation. The fetal intestines accumulated some of the PCB material, depending on the structure of the chemical, and after the birth, the chemical was cleared from the intestines. This observation indicates that the intestines may be an important target for PCBs.

Studies using exposed laboratory animals allow researchers to examine the exact effects of environmental toxins on intestinal function as well as on other organs in the body. It also allows scientists the opportunity to detect dysfunction and improve methods of treating these problems quickly and accurately. ■

Epidemiologic Research Sheds Light on Causes of Urinary Tract Infections

By Catherine R. Powell

"Acute urethral syndrome, cause unknown," is the catch-all diagnosis in about half the women who visit their physicians each year complaining of urinary pain—dysuria—and frequent urination. At the University of Washington School of Medicine, Dr. Walter Stamm and his associates—partially supported by the National Institute of Allergy and Infectious Diseases—undertook a research project to study the common variables and possible causes of lower urinary tract infections in the more than 2 million women who suffer from this disorder.

After eliminating those patients with urethral distress associated with identifiable causes such as vaginitis, gonococcal or herpes infections, Stamm's team evaluated the epidemiological and clinical aspects of 94 patients complaining of dysuria and frequent urination. Also included in the study were the characteristics of 66 normal women.

Of the 94 afflicted women, 35 appeared to be suffering from bacterial bladder infections, called cystitis. This condition is readily identified by significant counts of the normally culprit bacteria, and the presence of leukocytes, or white cells, in the urine, known as pyuria.

The other 59 patients exhibited less than the traditionally significant levels of urinary bacteria and would normally be categorized under the label of urethral syndrome. Stamm's researchers found that the two most common infectious agents in these patients were *Escherichia coli* and *Chlamydia trachomatis*. Neither of these microbes had been previously established as associated with this type of ailment, although *E. Coli* has been under suspicion.

By characterizing epidemiological and clinical profiles of the patient's symptoms and history, the Seattle team developed diagnostic clues to aid the clinician in identifying the invading organism in such urethral syndrome cases.

For instance, the study demonstrated that *C. trachomatis* may be a causative agent, as it is in nongonococcal urethritis in males. Indeed, the researchers suspect that *C. trachomatis* may be sexually transmitted, since the patients with this form of infection more often reported a new sex partner in the month before symptoms appeared. Many of these women used oral contraceptives more frequently than the normal population and less frequently had a history of urinary tract infection in the previous two years, than did the other urethral syndrome patients. The chlamydial infections also differed in the more sudden onset and the longer duration of symptoms, as well as the relative degrees of pyuria and hematuria (blood in the urine).

The implication of *E. coli* as a cause of urethral syndrome led the researchers to re-examine the traditional criteria for "significant bacteruria" (number of microorganisms in the urine). Clinicians currently consider a bacterial count greater than 10^5 microbes per milliliter to be indicative of cystitis. The Seattle team found that a lesser concentration (even 10 to 10^3 bacteria per milliliter), especially coupled with signs of pyuria, may be a sufficient indicator of serious infection. (In fact, it has been recommended by a reviewer of this study that the problem be renamed the pyuria-dysuria syndrome.)

Stamm and his team suggest that the varying bacterial counts may be explained by several circumstances. These factors include urinary dilution due to forced fluids and rapid urine flow, early or late stage of infection, high urinary pH, or a balance in the battle between the invading pathogen and host-defense mechanisms.

The Seattle report concluded that women with definite lower urinary tract infections could usually be divided into four groups: those with greater than 10^5 bacterial counts (considered cystitis), those with less than 10^5 bacterial counts, those with chlamydial infections and the one group with still no identified cause.

The three groups with known bacterial infections should respond to general antimicrobial therapy, such as tetracycline or sulfonamide treatment. More than specific treatments, Stamm's study emphasized the diagnostic importance of urinalysis to determine levels of pyuria, as well as urine cultures to target the specific bacterial pathogens to be counteracted.

A report of the study's results appeared in the August 21, 1980, issue of the *New England Journal of Medicine.* ■

Anaerobic Bacteria Appear to Cause Many Cases of Non-Specific Vaginitis

By Jody Dove

Researchers believe they have discovered the cause of non-specific vaginitis, one of the common genital infections afflicting thousands of women each year. Anaerobic bacteria (bacteria that survive without oxygen) and another species of bacteria known as *Gardnerella vaginalis (G. vaginalis)* are the causes of the disease, according to researchers from the University of Washington, the U.S. Public Health Service Hospital in Seattle, and the Seattle-King County Department of Health.

G. vaginalis has been linked to non-specific vaginitis in the past. But the finding of anaerobic bacteria in the vaginal fluid of women with non-specific vaginitis represents an important discovery about this mysterious disease.

The scientists were able to pinpoint the presence of anaerobic bacteria and *G. vaginalis* through a study they conducted on 97 students who were being treated for vaginitis at the University of Washington Student Health Center Women's Clinic, and 31 women who referred to either that clinic or to the Haborview Medical Center Vaginitis Clinic. After examination of the patients' vaginal fluid, the researchers confirmed the presence of non-specific vaginitis in 53 of the women, and the remainder served as controls.

Two methods were used to test the womens' vaginal fluid—gas—liquid chromatography, and quantitative anaerobic cultures. Gas-liquid chromatography displays patterns of volatile and nonvolatile organic acids contained in liquid. These chromatographic patterns revealed differences in the chemical make-up of the vaginal fluid of the normal women and the women with non-specific vaginitis.

In normal vaginal fluid, lactate is the main acid and the main organisms are lactate-producers. But in the fluid from women with non-specific vaginitis, the amount of lactate was decreased, and high levels of succinate, acetate and butyrate and succinate-producing organisms were found. This high ratio of succinate to lactate is a useful indicator in diagnosing this condition. Furthermore, the researchers detected in this fluid an increased amount of acetate, a fatty acid, which is produced by *G. vaginalis*.

The presence of anaerobic bacteria was borne out when the researchers treated the women who had non-specific vaginitis with metronidazole, a drug known to be effective against anaerobic bacteria, although it is not as beneficial in treating *G. vaginalis*.

Samples of vaginal fluid from the women with non-specific vaginitis were tested on the first day of treatment, and then, after 7, 21, and 42 days to determine the effectiveness of the metronidazole. Improvement in these women after metronidazole therapy correlated with the elimination of the anaerobic bacteria from their vaginal fluid.

It is still unclear, however, how anaerobes and *G. vaginalis* cause non-specific vaginitis. While it is now known that certain anaerobes act with *G. vaginalis* in causing non-specific vaginitis, the researchers are unsure whether one bacteria colonizes first, or whether one organism simultaneously stimulates the growth of the other.

It is also unknown which women are more likely to contract non-specific vaginitis. Sexual transmission could be a cause, as well as different methods of contraception. In addition, changes in the microbes found in vaginal fluid due to the estrous (ovarian hormonal activity) cycle or the menstrual cycle could be responsible.

Before a definitive answer can be attained, further studies of the epidemiology, microbiology, and biochemistry of non-specific vaginitis are needed.

This study was funded in part by the National Institute of Allergy and Infectious Diseases, National Institutes of Health. ■

Three Former NIH Researchers Win Nobel Prize

By Christine Krutzsch

The recent Nobel Prize in Physiology or Medicine recognizes three eminent immunologists; George Snell, Jean Dausset and Baruj Benacerraf. All three have had associations with NIH's National Institute of Allergy and Infectious Diseases (NIAID) in the form of research grants or contracts, and all have made important contributions to NIAID's immunology program.

Dr. Benacerraf was Chief of the NIAID Laboratory of Immunology during the years 1968 through 1970. He received the Nobel Prize for his pioneering work on immune response genes, a series of studies done in the 1960's and early 1970's. These studies led to further work by Dr. Benacerraf and others that helped to clarify the role of immune response and related genes in several areas of immunobiology and medicine. The inbred guinea pig colony of NIH was an important element in some of the research.

Part of the prize winning work was done at the NIH and part at New York University. Two NIAID intramural scientists, Drs. Ira Green and William Paul, who worked with Dr. Benacerraf in both institutions, collaborated closely in several of the key papers. Dr. Paul succeeded Dr. Benacerraf as Chief of the Laboratory of Immunology.

Before coming to NIH, Dr. Benacerraf held a professorship in pathology at New York University. For 10 of his 12 years at NYU, he received two research grants from the NIAID, one of which directly supported his early work on immune response genes.

In 1970, Dr. Benacerraf became Chairman of the Pathology Department at Harvard Medical School. During 1970-1977, he was awarded an NIAID research grant for studies in immunological responsiveness and an NIAID training grant in immunology and immunopathology. Since 1978, Dr. Benacerraf has had an NIAID program project grant in lymphocyte biology.

Dr. George Snell spent the majority of his research career, from 1935 until his retirement in 1969, at the Jackson Laboratory in Bar Harbor, Maine. During the 1940's and 1950's he described the histocompatibility genetics of the mouse, the so-called "H-2" antigen system, for which he won the Nobel Prize.

The mouse antigens were the first known transplantation antigens—markers that confer a biologic uniqueness on the tissue cells of each individual and distinguish self from non-self. The histocompatibility (tissue compatibility) antigens stimulate graft rejection in animals who receive skin or organ transplants from genetically dissimilar donors.

Dr. Baruj Benacerraf, chairman of the Pathology Department of the Harvard Medical School shared the 1980 Nobel Prize in Medicine with Dr. George Snell, a staff scientist at the Jackson Laboratory in Bar Harbor, Me., and Dr. Jean Dausset, the head of the Department of Immunology at the University of Paris. NIH PHOTO #1657

Dr. Snell was also instrumental in establishing many lines of inbred mice that have precisely defined H-2 genes, and the Jackson Laboratory has been a source of animals and typing sera that has served the immunology research community for many years.

Dr. Snell, in a contract extending from 1965 to 1973, was one of the first contributors to the NIAID Serum Bank that was established in 1965. This Bank provides standard reagents for tissue typing for both basic research and clinical purposes. It has been a valuable resource to kidney transplant teams.

Jean Dausset, a French physician, was honored for his discovery of the first *human* major histocompatibility antigens in the 1950's and for his work demonstrating their role in transplantation.

The importance of his work was recognized early, and he successfully competed for NIH support in 1961, receiving a NIAID research grant that has continued to the present day. Also, Dr. Dausset had a 3-year contract (1965-68) to provide human tissue typing reagents to the NIAID Serum Bank. ■

Custom-Made Glasses Allows the Severely Disabled to Communicate

By Susan Gerhold

Stephen Hefner, a young quadriplegic, is able once again to communicate with the outside world even though he can only move his eyes.

A team of electrical engineers from the Denver Research Institute (DRI), a department of the University of Denver, developed a new ocular control device to enable severely disabled or nonverbal patients to communicate and perform daily activities.

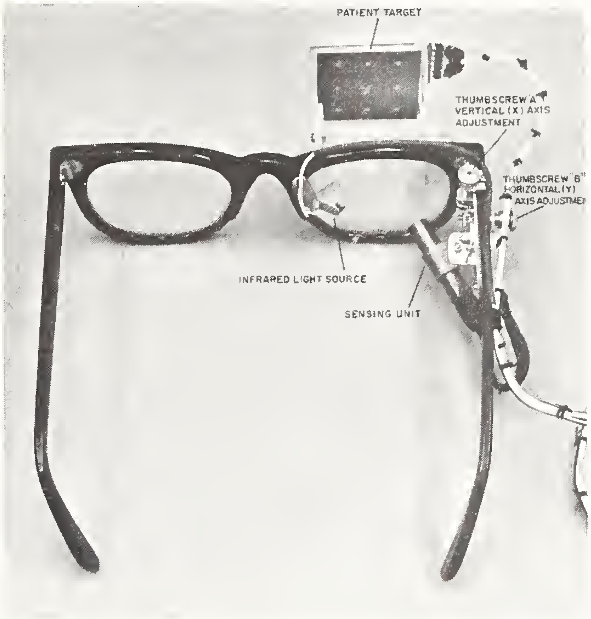
Stephen was hitchhiking one night on a dark road in North Carolina when a drunken driver accidently hit him, severing his spinal cord and leaving him completely paralyzed. Unable to move, speak, or even breathe without assistance, Stephen's only communication with his family was through eye movement. His father developed a primitive system for Stephen to blink his eyes for certain responses. This limited link to communication would later help Stephen to work with DRI researchers in developing a more advanced communications system.

With a grant from the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD), DRI researchers George Rinard and Owen Barns, built a special pair of glasses, complete with computer hook-up, a transmitter and a receiver built right into the frames. A system was designed using the positions within a 3x3 grid of squares on a screen. By selecting a predetermined sequence of squares on the grid, a variety of phrases and the alphabet can be uniquely determined. Currently, 32 letters and phrases are coded into the system. The grid is built several inches in front of the glasses frames so Stephen can see it clearly. Also located on his glasses frames are a small infrared light source and a sensing unit.

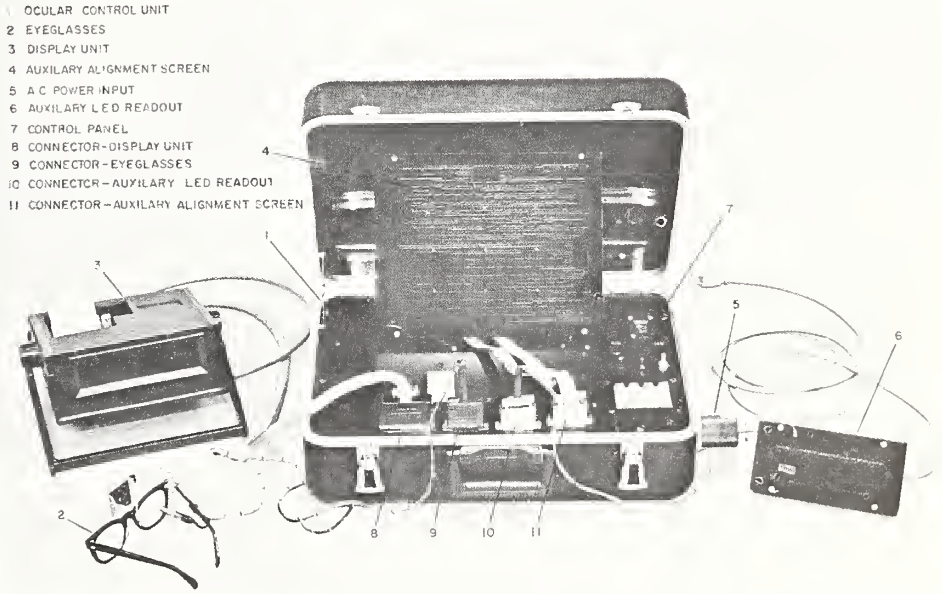
Stephen moves his eye to one of the nine grids where the letter is located, then back to the center grid, and then to the exact location of the letter he wants to spell. His eye movements are monitored by the infrared light which strikes his cornea and is then recorded by the sensing unit and fed into the computer. Finally the letter is decoded and printed out and the process begins again.

Rinard and Owens decided that Stephen needed more than just a print-out of his spelled words, he needed a voice, or auditory feedback. So a "Speak and Spell" children's game designed by Texas Instruments was added to the program. Stephen continues to spell out the letters with his eyes and each movement is decoded by the computer. However, the letters are now fed into the "Speak and Spell" where they are registered letter by letter, and then played back as an entire word.

Currently, Stephen has returned to his home in North Carolina, and continues to work with the DRI researchers in perfecting this device. According to Rinard, patients suffering from amyotrophic lateral-sclerosis (ALS), cerebral vascular accidents, cerebral palsy or strokes are likely candidates for an ocular control device similar to Stephen's. ■


PATIENT TARGET
THUMBSCREW "A" VERTICAL (X) AXIS ADJUSTMENT
THUMBSCREW "B" HORIZONTAL (Y) AXIS ADJUSTMEN
INFRARED LIGHT SOURCE
SENSING UNIT

Stephen's eye glasses are custom made. The infrared light source is placed to the left of the right eye so it can emit the light as the cornea moves. The sensing unit is placed on the right frame to pick-up the infrared signals. The grids are placed several inches from Stephen's eyes for easier reading. NIH PHOTO #1658



The computer hook-up, the "Speak and Spell" game, and the grid fit comfortably inside a suitcase for easy accessibility and travel. NIH PHOTO #1659

Cardiac Irregularities Associated with Liquid-Protein Diet

By Catherine R. Powell

Liquid protein diets, though effective in achieving weight loss, sometimes cause life-threatening cardiac irregularities (arrhythmias), according to a research team at the University of Rochester. Although some arrhythmias are benign, such induced abnormalities, if sustained, could possibly lead to further heart problems, even cardiac arrest.

Under a study carried out in the University of Rochester General Clinical Research Center, a special hospital unit funded by the NIH's Division of Research Resources, scientists at Rochester recommend emphatically that "protein-supplemented fasts as currently prescribed should be terminated pending further studies of the cause and prevention of such cardiac arrhythmias."

More than one-fourth of Americans over 30 years of age suffer from obesity greater than 20 percent above their ideal body weight. Liquid protein diets have been efficient in achieving weight reduction as shown in one study where 405 of 519 obese patients lost as much as 40 pounds in as little as six weeks.

Popularized in the late 70's, mainly by the 1976 publication of *The Last Chance Diet,* liquid protein diets were estimated to have more than 100,000 users, for one month or more, in 1977 alone. In that same year, at least 60 persons who were following this regimen died of heart complications. For all of these victims, electrocardiographs were available and all 11 showed accelerated heart rates (specifically ventricular tachycardia) in abnormal patterns. Autopsies of these patients revealed atrophy of the heart muscle tissue as is observed in starvation cases.

The Rochester research effort, led by Dr. Rafael Lantigua, studied five women and one male, ranging in age from 21 to 49, who weighed an average of 65 percent over ideal body weight. The researchers monitored these subjects in a control period of eight days, checking them for normal blood chemistry, heart function, and general health.

Then, during the 40-day experimental phase, the patients received a liquid protein (Pro-Fast by Robert Corporation, chosen for its widespread usage), in daily amounts specific to each subject's ideal body weight. The research team constantly supervised the subjects, and took urine, stool, and blood samples at regular intervals. They also administered weekly electrocardiographs. In addition, a mobile recording device (Holter) was used to monitor heart functions over a 24-hour period throughout the experiment.

Lantigua and his associates found that three of the six subjects showed serious cardiac arrhythmias during at least eight of the 16, 24-hour recordings taken during the experimental phase. These irregularities did not appear on the interval electrocardiographs.

The male patient demonstrated mostly normal heart rhythms, except for one recorded period of sustained ventricular bigeminy (paired pulses) and an episode of paired premature contractions of the ventricle.

Lantigua's team terminated another patient's fast when, after 26 days of normal recordings, she experienced an episode of ventricular tachycardia (heartbeat over 100 beats per minute). Continued monitoring after resumed normal diet revealed no residual abnormalities.

Two particularly alarming aspects of the Rochester research study showed that cardiac irregularities occurred as early as 10 days after beginning the protein-supplemented diet, and that the arrhythmias were not detected by repeat-interval electrocardiographs. Routine chemical tests and metabolic balance studies also failed to identify or predict those patients with a higher risk of cardiac complications.

Since only the 24-hour monitor revealed the arrhythmias, it is possible, even likely, that a liquid protein dieter who is checked routinely as an outpatient, may have undetected cardiac arrhythmias.

In other studies, scientists have suggested that deficiencies of protein, electrolytes, trace elements, and essential fatty acids may cause the cardiac abnormalities in such dieters. Other researchers have found in animal studies that supplementing the diet with minerals and micronutrients, has been beneficial. However, no human research has been conclusive in this regard. Due to its limited size, the researchers could not substantiate these theories.

Lantigua and his associates did conclude most definitely that the prescription of liquid diets should be suspended until further studies have been performed on its casual relationship to cardiac arrhythmias.

For additional information, consult the report published by Lantigua, et al, in *The New England Journal of Medicine,* 25 September 1980 Vol. 303, No. 13, 735-8. ■

Studies of Hormonal Requirements of Endometriosis Yield Clues to Treatment

By Susan Johnson

Although birth control pills and other compounds that mimic the action of progestrone are the most commonly prescribed treatments for endometriosis, other therapies may be more effective, a study by the National Institute of Child Health and Human Development suggests.

Endometriosis is a disorder in which uterine lining, or endometrium, is found growing outside the uterus. Like normally located endometrium, the extrauterine tissue proliferates during the menstrual cycle and breaks apart at the end of the cycle if conception does not take place.

Unlike normally located endometrium, however, it is not discharged during menstruation. Extrauterine endometrial tissue bleeds into the abdomen, causing inflammation and scarring.

Endometriosis accounts for 10-20 percent of all female infertility. Although the disease has been studied for decades, the hormonal requirements for its initiation and maintenance are not fully understood.

It is known that hormones secreted by the ovaries are necessary for the establishment and/or continued presence of endometriosis, because the disorder occurs only after the onset of puberty and disappears after menopause. It is also known from previous research, that estrogen supports the growth of endometrial tissue outside the uterus.

In studies with monkeys whose ovaries had been removed, investigators in NICHD's Pregnancy Research Branch have discovered that while ovarian hormones are necessary for the persistence of endometriosis, they may not be required for its initiation. They have also found that the ovarian hormones, estrogen and progesterone, alone or in combination, can support the growth of extrauterine endometrial tissue.

The scientists implanted endometrial tissue in the abdomens of the monkeys, then divided the animals into four groups. A control group received no supplemental hormones, a second group received estrogen, a third received progesterone and a fourth received both estrogen and progesterone.

After 4 weeks, endometriosis was detected in all groups. By 12 weeks, the endometrial tissue in the control monkeys were no longer growing. The tissue in the other three groups remained viable throughout the 16-week study.

These findings suggest that birth control pills, which contain estrogen and progestin, and other progesterone-like agents may actually support endometriosis.

The therapeutic value of birth control pills probably lies more in their ability to prevent retrograde menstruation than in suppression of ongoing disease, the scientists noted. Retrograde menstruation, the backward flow of menstrual blood through the fallopian tubes into the abdomen, is believed to account for most cases of the disease.

The best treatment for endometriosis would be one that simultaneously suppresses the secretion of ovarian hormones, thereby shrinking existing endometrial tissue, and inhibits retrograde menstruation, concluded the investigators. Reported successes with danazol, a drug which shuts down production of ovarian hormones and stops menstruation, are consistent with their interpretation.

This study was reported by Dr. Gere DiZerega, Donald Barber, and Dr. Gary Hodgen in the June, 1980 issue of *Fertility and Sterility.* ■

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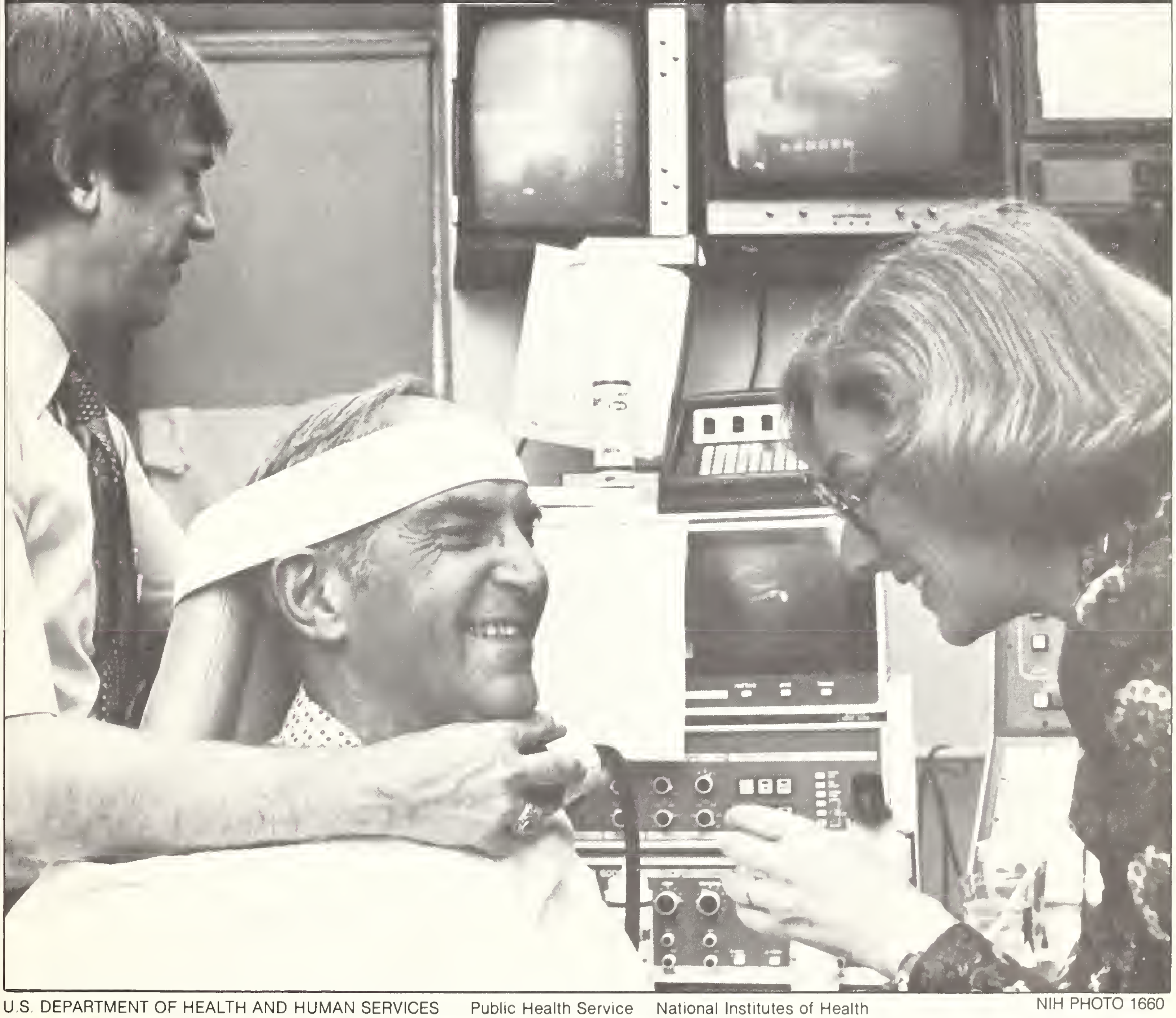

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NIH PHOTO 1660

News&Features
from NIH

March 1981

One woman's personal account of her battle with lupus has inspired many other victims of this mysterious disease. Scientists at NIH are carrying out extensive studies to understand the causes and mechanisms behind lupus, which affects many more women than men.

See page 2.

Barbara Sonies, speech language pathologist at the NIH Clinical Center, works with patients who find themselves with speech or swallowing problems after surgery or as a result of their disease. Using adapted ultrasound equipment, she can watch the patient swallow, chew and pronounce sounds. After observing these tasks, Ms. Sonies can review instant photos to identify the problem and plan her course of therapy.

See page 4.

Researchers at a prominent Massachusetts hospital have found that some obese people will stay overweight for the rest of their lives, despite diets or other weight loss programs. These people appear to have an enzyme deficiency that interferes with their ability to burn up calories.

See page 3.

The technique of fusing cancer cells with lymphocytes may be the basis for a simpler, cheaper test to determine which breast cancers are dependent on hormones for their growth. Eventually, it may be a more practical tool for deciding proper therapy for the thousands of women who have this disease.

See page 6.

Neurofibromatosis—the Elephant Man's Disease—has attracted the interest not only of drama critics, but of medical researchers as well. The NIH Inter-Institute Genetics Clinic evaluates some of these patients in the hope of identifying clues to the variability of this disease and its link to cancer.

See page 11.

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Research Gives Hope to Patients With Lupus

by Susan Gerhold

Henrietta Aladjem, signs autographs for her book "The Sun is my Enemy," which was published in 1972. As a "one woman advocate" Ms. Aladjem lectures all over the world, is a member of the National Allergy and Infectious Disease Council at the NIH, a member of the board of directors of the Lupus Foundation, honorary chairman of the Lupus Erythematosus Foundation of Massachusetts and the editor of *Lupus News,* a quarterly publication, put out by the Lupus Foundation. She is currently writing another book—"Lupus—Hope Through Understanding."
NIH PHOTO 1661

When you first meet Henrietta Aladjem, a very attractive, fair-skinned blonde with bright blue eyes, she seems to be the picture of perfect health. However, Ms. Aladjem has a very serious disease, which can be fatal. According to the Lupus Foundation, approximately 1 million Americans are affected and 5,000 die annually. Women of child-bearing age are most susceptible, and it occurs in women 10 times as often as in men. Nearly 50,000 new patients each year become victims of this disease.

Ms. Aladjem has "Lupus" or Systematic Lupus Erythematosus (SLE). Lupus is an inflammatory generalized disorder that affects the connective tissues of the body, the tissue that "glues" the cells of the various organs together and provides support for the entire body. It is apparently caused by abnormal antibodies present in the circulation which become trapped and injure a number of different organs of the body.

The first sign of lupus may be joint pain, an unexplained fever, or a rash that appears over the cheeks and the bridge of the nose. This butterfly-shaped rash often occurs when a patient has been exposed to the sun.

Ms. Aladjem has been in remission; or with no signs of the disease, for several years. Sometimes lupus appears mysteriously if the patient is not severely affected and it may disappear especially after menopause.

A chronic inflammatory disease, lupus may affect any organ in the body. It has been found that the disease is sometimes triggered by infection, stress, exhaustion, sunlight, or even ultraviolet light.

Since the disease affects people in different ways, physicians sometimes are unable to diagnose the disorder immediately. Patients may feel fatigued, or aching joints, run fevers, experience weight loss, or anemia and occasionally suffer mental or emotional problems.

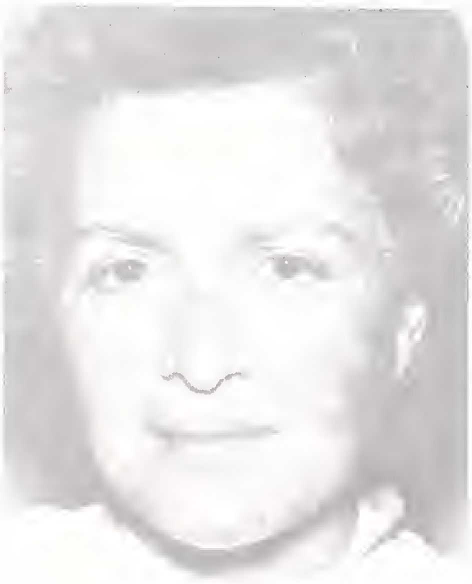
In the 1950's Ms. Aladjem's physicians were very puzzled by her condition. Prescribed drugs did not help her and each day another ailment would appear. The cold weather made her joints ache; the hot Florida sun gave her a rash; aspirin made her stomach upset; and the list grew longer. Finally, after seeing a hematologist in a leading Massachusetts hospital, her blood tests revealed for the first time a small lupus or LE cell. This is a white cell that eats the nucleus of other white cells, which have been coated with an antibody. It is a feature of most lupus patients, and is one of many autoimmune features.

The presence of autoantibodies such as antinuclear antibodies help physicians recognize the disease. Such autoantibodies support the idea that lupus is an "autoimmune disorder," which means the body's immune system produces abnormal proteins that bind to the body's own constituents. This often leads to an attack by the immune system against vital organs and results in disease symptoms.

Her doctors had not seen many cases of lupus, and those they had seen were in the terminal stages of the disease. Often, their prescribed "wonder drugs" gave Ms. Aladjem severe reactions and her symptoms worsened. Then, cortisone, a hormonal drug that has brought prolonged life to many, as well as a state of remission to others, was prescribed. Her condition improved and her life returned to normal.

Since her remission, Ms. Aladjem has travelled extensively to find cures, new treatments, anything to build a little hope for herself and countless others suffering from this disorder. Today, with her help, organizations have been formed to give advice to lupus patients. Medical research on lupus has enabled physicians to detect the disease more rapidly and to begin treatment before the disease progresses.

Scientists continue to concentrate on what causes the disorder, and how it progresses in the body. At the NIH, two institutes, the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) and the National Institute of Allergy and Infectious Diseases (NIAID)



The butterfly rash appeared on Ms. Aladjem's cheeks and nose after she had spent time in the warm Florida sun. The rash is one of many signs that may appear in lupus patients prior to medical therapy. NIH PHOTO 1662

After medication, Ms. Aladjem's face cleared up and she is now very careful about being exposed to the sun. Often, a lupus patient will have to rearrange his lifestyle somewhat so as not to disrupt the body's system, causing a crisis, such as the butterfly rash or a fever.
NIH PHOTO 1663

are currently working on several different aspects of lupus research.

Dr. Alfred Steinberg, Arthritis and Rheumatism Branch, NIAMDD, and his staff have provided evidence that lupus may be a multifactorial disease. Lupus appears to be caused by a combination of genetic, immune, environmental and hormonal factors. Their research focuses upon the cellular basis of illness in both patients and the very useful mouse models of the human disease. Their studies indicate that different cells may be responsible for different aspects of the disease, and that different autoantibodies may be responsible for different symptoms. In addition, they are elucidating the genetic basis for some of the autoimmune abnormalities.

Another aspect of Dr. Steinberg's research is evaluating newer methods of treatment in mice before using them in patients. The New Zealand mouse models of SLE have been used to test hormonal therapy, anti-viral drugs, and immunosuppressive drugs in different combinations. All of those modes of treatment have been tried subsequently in patients. In addition, more specific therapies are being tried; however, none are yet ready for human study.

The current clinical studies in the Arthritis Branch involve carefully controlled evaluation of new forms of therapy by use of randomized trials. Such studies allow the physician-scientists to fully evaluate the relative therapeutic benefits and toxicities of new treatments.

Dr. James Balow and his staff in the clinical nephrology group, another section in the Arthritis and Rheumatism Branch, are evaluating the role of the kidney biopsy in SLE. They have developed a scoring system which combines light, fluorescence and electron microscopy to better follow the progress of kidney disease in patients, and to improve methods of evaluating new treatments.

Another facet of lupus research is being done by scientists in NIAID. Dr. Ira Green and Dr. Anthony Fauci and their colleagues have been collaborating with Dr. Alfred Steinberg in the analysis of immune regulation in patients with SLE. These studies indicate that patients with SLE have defects in normal immune regulation. Some of these abnormalities are brought about by antibodies which preferentially bind to suppressor cells. It is theorized that in the absence of normal immune regulation by suppressor cells, the SLE B cells become hyperactive and produce excessive antibody, including autoantibody.

In 1953 when Ms. Aladjem was stricken, 50 percent of lupus patients died within four years after diagnosis. Currently, nearly 90 percent will live 10 years or more after diagnosis, due to early detection, aggressive treatment and the vast new knowledge researchers have acquired from the animal and clinical trials. ■

Some Overweight People May Blame Their Obesity on Reduced Enzyme Levels

by Susan Gerhold

New studies on obesity indicate that some people may never lose weight in spite of vigorous dieting, drugs or vitamin programs.

Under a grant by NIH's Division of Research Resources (DRR), Dr. Jeffrey Flier, Chief, of the Diabetes and Metabolism Unit at Beth Israel Hospital, and his colleagues, have discovered that "people differ remarkably in the way their bodies handle food."

Clinical trials began after Dr. Flier and his staff reviewed test results of an animal model, the obese mouse. These laboratory animals demonstrated a reduced level of sodium-potassium ATPase or the enzyme, adenosine triphosphatese, in the liver and muscle.

ATPase works like a small pump, transporting sodium and potassium in the body. When working properly, ATPase uses energy and burns up calories. These results suggest a possible biochemical defect in the production of heat (cellular thermogenesis) or the rate of energy used to burn up calories. This theory may be an important variable in why some individuals and test animals remain overweight.

Dr. Flier and his colleagues recruited 28 healthy volunteers and 23 obese patients from the Endocrinology Clinics at Beth Israel and the New England Deaconess Hospitals in Boston.

Fifteen of the 23 obese patients were studied in three to seven months after they ate a supervised diet. Of these, 12 had lost weight, an average of 18 percent of what they weighed at the beginning of the study. Blood samples were taken to measure ATPase in erythrocytes (red blood cells). Results showed that the obese patients' ATPase levels were below normal by 20 percent, suggesting a defect in the sodium-potassium pump. Even more remarkable was the evidence that the heavier the patient, the lower the ATPase level.

Other findings showed that 40 percent of the obese patients had sodium-potassium ATPase levels lower than all of the normal controls except one, and that 20 obese patients had levels lower than the average of the normal volunteers.

However, two of the obese subjects had enzyme levels higher than those in the control group, suggesting that the reduction in sodium-potassium ATPase units does not result from the development of obesity alone.

Flier and his colleagues are unable to correlate at this time whether the sodium-potassium ATPase deficiency is related to the development of obesity or whether it is a consequence of established obesity. However, the latter theory is demonstrated in two different studies. One obese patient who had been heavy since early childhood had the highest enzyme level (twice the average of the normal controls' level) but continued to gain weight. His ATPase pump was not operating efficiently even though the enzyme level was high.

Also, in results from an unpublished paper, Flier and his team studied normal mice on an excessive calorie diet. They found the sodium-potassium pump activity in the livers of the mice had increased by 120 percent just to keep up with the rich new diet. Their system was working correctly and efficiently.

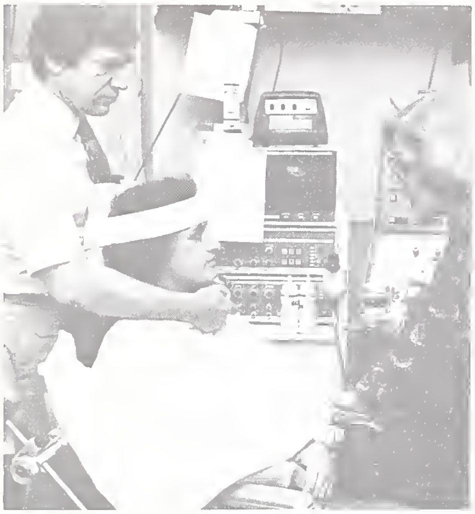
Future studies according to Flier will include focusing on the sodium-potassium defect and correlating the findings with the levels of enzymes in other important tissues. "If we can find a correlation, the erythrocyte may be useful in identifying patients with a possible enzymatic defect associated with obesity," said Flier.

In addition the team plans to study why the altered metabolism of food by the body is another reason for obesity, not just overeating.

Dr. Flier's paper has been published in the *New England Journal of Medicine* October 30, 1980, Volume 303. ■

NIH Speech Pathologist Uses Ultrasound Equipment to Detect Speech Problems

by Susan Gerhold



Roberta Dekelbaum, a normal volunteer, is very familiar with the volunteer program at NIH. Her grandfather began as a volunteer almost 15 years ago and her grandmother was the first woman normal volunteer in the Baltimore Longitudinal Study of Aging. Currently, Roberta's mother is a volunteer and her husband and father have applied as volunteers. During her visit to the Clinical Center, Roberta repeats sounds to Barbara Sonies, as Dr. Shawker moves the transducer throughout the throat region. NIH PHOTO 1664

Patients suffering from esophageal cancer, amyotrophic lateral sclerosis, strokes, seizures, Parkinson's Disease, or central nervous system tumors, often have problems with talking, swallowing or chewing; all daily occurrences that healthy individuals take for granted. Now, at the NIH's Clinical Center, these individuals may be helped by speech language pathologist, Barbara Sonies, while being treated for their original disorder.

Ms. Sonies works with other NIH clinical staff when conducting various research protocols. In one instance, normal controls or healthy volunteers participating in an aging study at the National Institute on Aging, Baltimore Gerontology Research Center, are involved in one of Ms. Sonies' research protocols on oral-motor problems. Ms. Sonies is working in conjunction with Dr. Bruce Baum of NIA on this study. Studying these healthy individuals allows Ms. Sonies and her colleagues to see speech patterns, observe swallowing and chewing under normal circumstances. With the critical assistance of Radiologist Thomas Shawker of the Clinical Centers' Diagnostic Radiology Department, Ms. Sonies is observing oral-motor dysfunction in patients suffering from those diseases mentioned above.

Ultrasound equipment that is regularly used to do procedures such as liver, kidney scans, or obstetrics, has been adapted to study speech and swallow patterns. The equipment has been modified with the help of electrical engineer Thomas E. Hall, of the Biomedical Engineering and Instrumentation Branch, DRS. This realtime B-scan (a two-dimensional continuously moving image) ultrasonic system is able to visualize the motions of the tongue during speech and swallowing.

This adapted system provides a harmless, noninvasive technique to patients and at the same time is reliable in assessing the lingual functions of the patient. Until this time, researchers subjected their patients to impossible and awkward procedures that often interfered with their normal articulation. This system allows the patient to speak without jaw restrictions or exaggerated head postures. It also enables the researcher to compare and retrieve multiple repetitions of speech samples in a digital format which can later be analyzed by computer.

With the real-time B-scan, Ms. Sonies and her colleagues can now observe a variety of neurological conditions such as those affecting the muscles and nerves controlling the tongue, palate, lips, pharynx, and larynx. The visualization of abnormal patterns of tongue movement, including tremor, is now possible. Ultrasound may potentially be useful in predicting oral-motor function problems that are often life-threatening to the elderly. These problems may appear as sleep and swallowing dysfunctions. If these problems are associated with changes in the tongue itself, then future treatment programs can be devised.

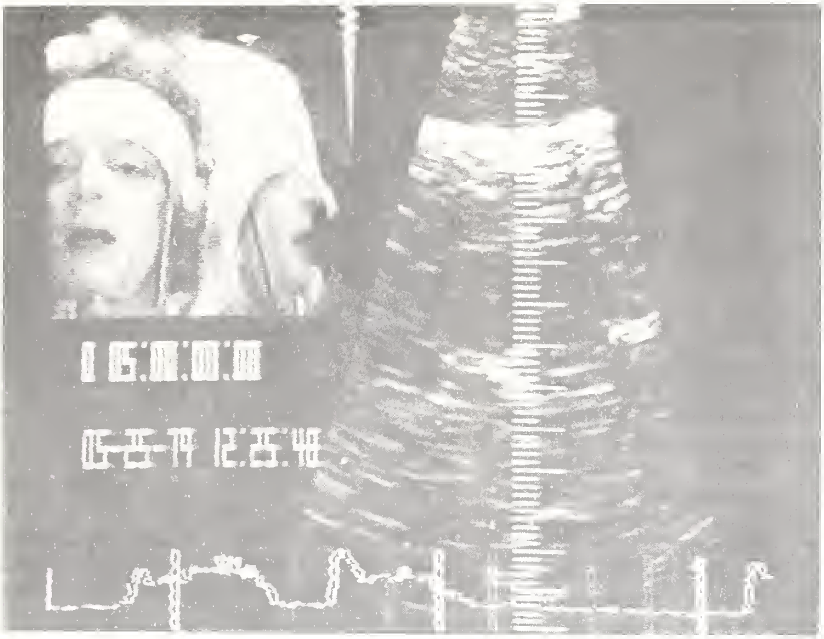
Along with this ultrasonic scanning system comes an array of sophisticated devices that include an adapted scanner, a closed-circuit television system that allows simultaneous monitoring of speech and ultrasonic signals, and a specially equipped wheelchair. The wheelchair is fitted with an adjustable headrest to allow for stable head support and correct positioning. It is also equipped with two mirrors that provide side and front views of the face. A microphone is positioned at the side of the chair close to the patient's mouth to record the patient's speech.

The hand held scanner is fitted with an "L" shaped plexiglass form which attaches to the transducer at the bottom of the "L" frame. The scanner is then placed under the patient's chin with the short area of the "L" extending six inches from the face and the long arm extending at a right angle parallel to the cheek. With this attachment, Dr. Shawker can rotate the transducer in various positions relative to the patient's tongue surface.

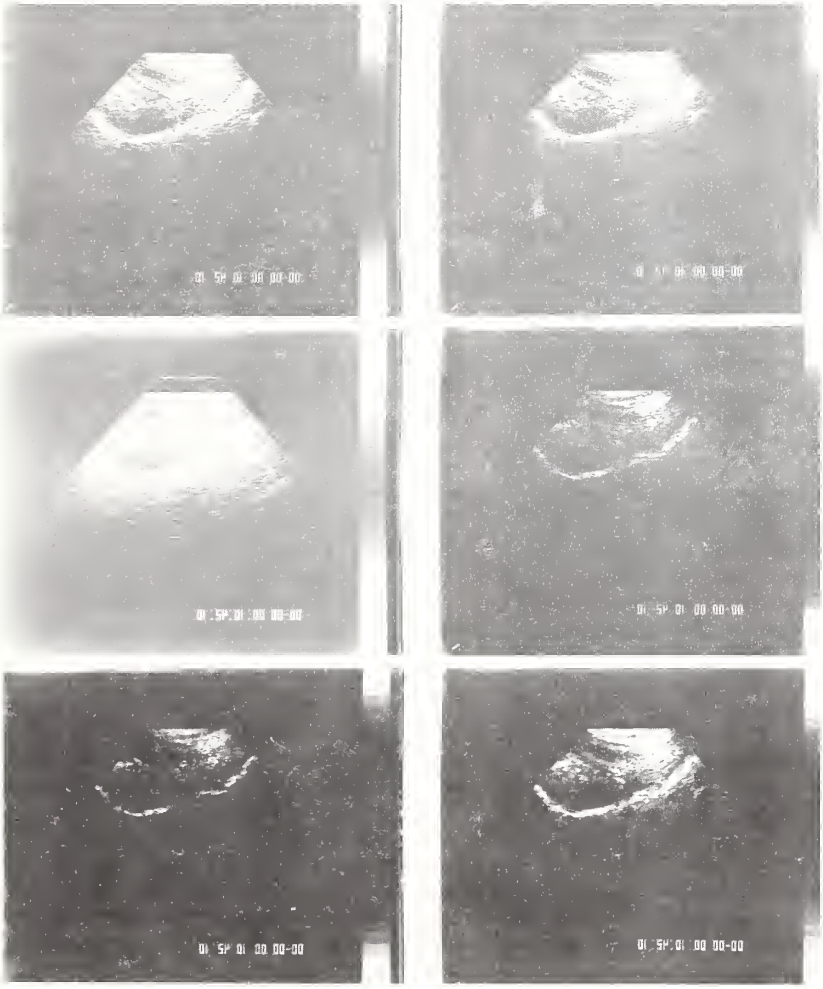
Ms. Sonies then asks her patients to repeat a set of phonemes such as /a,i,t,k/ and their combinations, in the form of syllables to test their ability to move the tongue when speaking. These particular phonemes were selected because they represent the range of tongue movements during articulation. A composite video image on a closed-circuit television system is combined with the patient's voice, front and side views of their face, the ultrasonic scan and the filtered audio signal. The composite is then recorded and stored permanently on videotape for later analysis.

Ms. Sonies and her colleagues are also studying ultrasound of the tongue as a biofeedback training technique in the treatment of articulatory and swallowing disorders. With this new scanning device, the radiologist, the neurologist, speech pathologist, dental researcher, and otolaryngologist will be able to use this system simultaneously.

For further information on ultrasound imaging contact Barbara Sonies, M.A. Clinical Center Rehabilitation Department, Building 10, room 5D37, or Dr. Thomas Shawker, Clinical Center Diagnostic Radiology Department, Building 10, room 6S211. ■

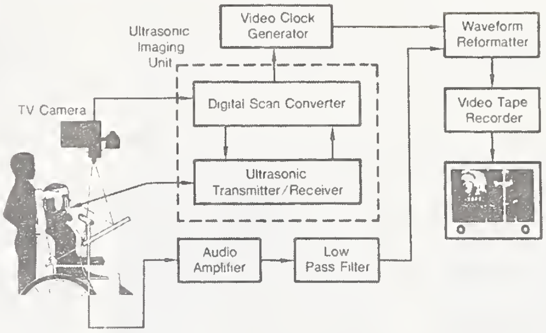


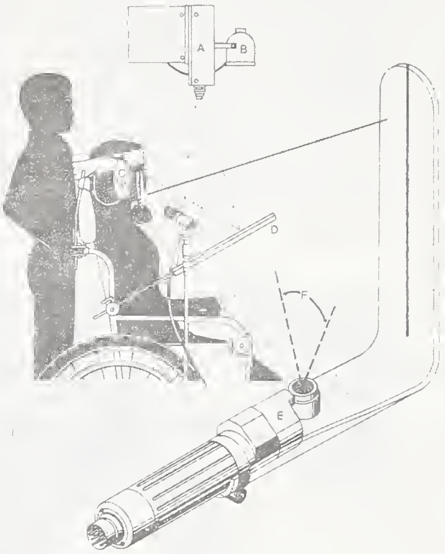
Ultrasound image of normal tongue motion is displayed when the patient says the sound /a/. The upper surface of the tongue is the white curved band extending across the middle of the sector. NIH PHOTO 1665



A patient's tongue moves while swallowing, talking, or chewing. The equipment used in the Diagnostic Radiology Department can take photographs of this movement. The curved white horizontal line in the middle of the picture is the tongue. The speech language pathologist can watch the patient and at the same time record the actions of the tongue with these photos. NIH PHOTO 1666

Block Diagram of the Ultrasonic Tongue Imaging System





Ultrasonic imaging of lingual motion: Diagram of placement A (video camera), B (infrared light), C (side view mirror), D (front view mirror), E (transducer with attachment to indicate angle of placement) and F (ultrasound sector).

New Estrogen Receptor Test May Assist Physicians in Treating Breast Cancer

by Helen Ou

By using the chromatography technique, Dr. Jensen, above, and Dr. Greene were able to separate hormone receptor proteins from many other proteins in the malignant breast tissue. NIH PHOTO 1667

The successful preparation of monoclonal antibodies that react to estrogen receptors has been reported by researchers at the University of Chicago. This advance could be useful in deciding the proper therapy for breast cancer patients whose tumors are hormone-dependent, and in understanding how hormones contribute to the development and progression of the disease.

Monoclonal antibodies may eventually be the basis for a new test to determine in advance which breast cancers are hormone-dependent and which are not. According to one of the investigators, Dr. Elwood Jensen, 25,000 of the more than 90,000 breast cancer cases that occur in the United States each year are hormone-dependent, that is, their continued growth depends on estrogens. Jensen says "Depriving these cancers of estrogen, either by surgically removing the hormone-producing glands or by administering drugs that antagonize the hormone's action, is the most effective means we have for treating breast cancer once it has become widespread throughout the body. But this therapy is of no value in patients whose tumors are not hormone-dependent and whose best recourse is cytotoxic (cell damaging) chemotherapy."

Determining which breast cancers are hormone-dependent is currently done by analyzing a sample of the breast tumor for a protein using a test known as "the estrogen receptor assay." This test was originally developed at the University of Chicago on the basis of studies by Drs. Jensen and Eugene DeSombre, who found that estrogens exert their hormonal actions by combining with the specific receptor protein in the target cancer cells. The test uses the radioactively-labeled hormone as a marker for the receptor to which it binds.

The National Cancer Institute has recommended that all breast cancers, both primary and metastatic, should have this analysis. Although receptor assays on breast cancer specimens are now carried out routinely at major medical centers throughout the world, there has been no simple, inexpensive way to perform the test. In addition, there is a need to eliminate shipping tumor specimens to a central laboratory, during which time the sensitive receptor protein can lose its ability to bind to labeled hormone.

The Chicago researchers used the hybridoma technique, developed five years ago by Milstein and Kohler in England, to produce monoclonal antibodies to estrogen receptors. This was done by fusing cancer cells from mice with normal spleen cells from rats, immunized with purified receptors, to produce antibodies. The resulting hybrid cell is a specifically tailored antibody, in this case, for the estrogen-receptor protein, with an endless capacity for growing in the laboratory. Antibody clones can then be grown in large amounts for study and other applications.

For this purpose, the antibody was labelled with radioactive iodine and used to identify the estrogen receptors in the breast cancer tissue. Because radioimmunoassays are already being used widely for the analysis of other biological substances, most hospitals already have the necessary facilities for counting radioactive iodine. Thus, the cost of the test should be reasonable and free from the technical difficulties that often impair the accuracy of methods that depend on binding of the labeled hormone as the marker.

A major accomplishment in developing the new monoclonal antibody technique by the Chicago researchers was the separation of a pure hormone receptor from many other proteins in the malignant breast tissue for injection into the rats.

Drs. Jensen and Greene at the University of Chicago are studying a Lewis rat for their research in producing monoclonal antibodies to human estrogen receptor. NIH PHOTO 1668

Greene and Jensen's method relies on a lab technique known as chromatography, where a column packed with beads is coated with a hormone, estradiol. These beads trap the receptor protein from the breast tumor preparation which is poured over the column. The column washings contain enough pure receptor to immunize the rats without further purifications.

"We couldn't have obtained the new antibodies without hybridomas and without the refinements in producing them developed by Dr. Thomas McKearn and Dr. Frank Fitch at the University of Chicago," says Jensen.

Greene and Jensen are working in collaboration with Abbott Laboratories in the production of monoclonal antibodies to human estrogen receptors on a large scale and in the development of a practical diagnostic kit.

This study was supported in part by a grant from the National Cancer Institute and a report on the research appeared in the *Proceedings of the National Academy of Sciences* (September 1980, pp. 5115-5119). ■

Animal Studies Show That Artificial Food Dyes Are Associated with Hyperactivity

by Mary Donovan

Animal studies indicate that certain food dyes interfere with chemical communication in the brain, adding further support to the theory that they are associated with hyperactivity in children.

At a recent meeting of the Nutrition Coordinating Committee, Dr. Ellen Silbergeld, Chief, Neurotoxicology Section, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) pointed out that contradictory information exists between studies in humans exploring the association of artificial food dyes with hyperactivity, and those in animals. Although artificial food coloring has been implicated in hyperactivity, it has not been proven to be the cause of this disorder, which, by some estimates, affects up to 5 percent of the school-aged population.

A typical hyperactive child displays uncontrollable, inappropriate behavior, marked by "over-reactive" responses and a short attention span. Ironically, amphetamines, also known as "speed", have been successful in producing a tranquilizing effect in many hyperactive children. Many scientists believe that there is a biochemical basis for hyperactivity, which, if identified, could perhaps be corrected.

Two different types of clinical trials have been done to identify the involvement of artificial food dyes in hyperactivity, and, as yet, neither one has supported the association. One approach involves eliminating foods known to contain artificial colors, and then to document the intensity and frequency of hyperactive behavior. However, since artificial coloring is found in so many foods, total elimination is virtually impossible.

With the other technique, known as a "challenge study," a cookie or glass of cola loaded with a variety of artificial colors is given to hyperactive children. This approach has been undertaken only on those children who responded favorably to the elimination diet. Because so few of these "challenged" children displayed any dramatic changes in behavior after receiving the cookie or cola, this type of study was also considered to be inconclusive.

Studies of artificial food dyes in humans are particularly difficult to undertake because we are constantly exposed to large amounts and, as yet, no one understands how these chemicals are metabolized by the body, where they are deposited and how long they stay in the body. In the laboratory, experimental animals, in this case, rats, offer a more controlled environment, where they can be fed or injected with specified amounts of dye and studied closely. Dr. Silbergeld and her group chose red dye #3 to investigate, in part, because it is currently the most commonly used red artificial coloring.

The researchers found that, in low doses, the dye enters the brain readily, inhibiting the uptake of neurotransmitters by nerve cells. Neurotransmitters are chemicals that convey messages from one nerve cell to another, regulating the activity of the nervous system. About three classes or neurotransmitters appear to be affected, but, as yet, scientists do not know which ones, if any, are more sensitive to the dye than others.

More specifically, the dye appears to interfere with neurotransmission by inhibiting the activity of the enzyme, Na-K ATPase, which is responsible for transporting and regulating sodium and potassium throughout the body. Interestingly enough, red dye #3 seems to interfere with the Na-K ATPase in the brain alone.

According to Dr. Silbergeld, these studies indicate that red dye #3 has a definite effect on the central nervous system—probably on the Na-K ATPase activity specifically. Since this enzyme is under genetic control, it may explain why so few of the hyperactive children responded to challenge with the artificial dyes.

The scientists are currently studying how red dye #3 binds to nerve cells by tagging the dye with a radiolabel, so it can be tracked on its journey through the nervous system. In addition, they are injecting the dye directly into the brains of the lab animals to allow for more direct observation of its behavior.

Dr. Silbergeld adds that "test-tube" studies are important to establish the toxic effects of these dyes before any definitive association can be made between them and hyperactivity. ■

Vaccine Against Pneumonia May Protect Patients with Sjogren's Syndrome

by Hilah Thomas

Research from the National Institute of Dental Research suggests that physicians treating patients with Sjogren's Syndrome (SS) may wish to consider vaccination to give them greater protection against pneumococcal pneumonia.

There are no reliable statistics on how many Americans endure the discomforts of SS, a condition in which a scarcity of secretions leaves eyes, nose, mouth and the linings of the respiratory and digestive systems abnormally dry. Immunologists believe it is second to rheumatoid arthritis among the autoimmune diseases in which patients react destructively against some of their own tissues. It may remain very mild with only dry eyes and mouth for many years, or it can progress fairly rapidly to other similar tissues. The cause of SS is unknown, as is the reason why there are nine females to every male victim.

Whereas synthetic tears, and various ointments and lotions can help to ease their discomfort, the risk to SS patients of certain other diseases, such as tooth decay and pneumonia, increases with the decrease of natural antibiotic secretions. In fact, the greatest problems in SS are complications such as pneumonia and septicemia. Another unexplained risk is increased likelihood of developing a lymphoma type of cancer.

Investigators at the NIDR thought that vaccination against various strains of pneumococcal bacteria might help SS patients. Before attempting to vaccinate, they wished to know whether patients with autoimmune diseases could develop antibody levels high enough to be protective and also whether vaccination would aggravate the SS symptoms.

After the doctors learned that patients with systemic lupus erythematosus, another autoimmune disease, had been safely and effectively vaccinated against influenza and pneumonia, they decided to test the effects of a pneumococcal vaccine among a group of SS patients.

Thirty-two females, 40-76 years of age, agreed to a trial in which half of them received injections of a vaccine prepared from extracts of cell walls of 14 strains of pneumococcal bacteria in a solution of salt water and phenol. The other half received only the solution. One week later the patients were questioned about any early reactions. Then one month and six months after injection, they were recalled for physical examinations and laboratory studies of blood, kidney function, muscle and liver enzymes, various immune reactions, and levels of antibodies against the 14 strains of bacteria.

The patients showed no ill effects of any injection on their underlying disease conditions. Some reported mild, transient effects such as brief fever or redness at the injection spot. The antibody levels in those who received only the solution remained the same for the six-month period after the injection as they were at the beginning of the trial. However, among those vaccinated, the levels of antibodies rose during the first month and remained protective, but somewhat lower, against most strains six months later. Serotypes 7, 8, 9, and 23 induced the most antibody while 12 and 14 were least effective.

These findings have convinced the physicians that vaccination could help to protect SS victims against most forms of pneumococcal pneumonia.

Drs. Jacob Karsh, Nicholas Pavlidis, and Haralampos M. Moutsopoulos, formerly of the NIDR, and Gerald Schiffman of the State University of New York, Downstate Medical Center, Stonybrook, report this research in *Arthritis and Rheumatism,* November, 1980. Dr. Karsh is now at the Royal Victoria Hospital, Montreal, Quebec, Canada; Dr. Moutsopoulos is at the University of Ioannina's School of Medicine, Ioannina, Greece; and Dr. Pavlidis is in Athens, Greece. ■

Drug Antigens May Be Useful in Predicting Penicillin Allergy

by Christine Krutzsch

One research area which is yielding valuable knowledge about the nature of drug allergy is the study of allergy to penicillin.

Some kind of hypersensitivity reaction is estimated to occur in about one of every 50 persons who take penicillin. Among such responses, about 76 percent are skin reactions, about 22 percent involve angioedema or other systemic reactions, and 2 percent are anaphylactic shock reactions. This translates into a rate of one case of anaphylactic shock for every 2500 penicillin-taking patients. Fatal anaphylactic shock is much more rare, occurring only in about one of every 100,000 courses of penicillin.

Until several years ago, penicillin allergy continued to be a perplexing problem for patients and physicians alike. Doctors were unwilling to give this drug to persons with past reactions to penicillin in concern that another allergic or anaphylactic reaction might occur, and there was no way to check whether this assumption was justified or not.

However, several NIAID grantees and other scientists, notably Dr. Charles Parker, Dr. Bernard Levine and Dr. Franklin Adkinson, have worked on the development of skin test materials that represent some of the different antigens formed as the penicillin molecule is processed by the body.

Two of the most common penicillin antigens were used in a study of over 1200 patients. The survey showed that among persons with a history of penicillin reactions, most lost their sensitivity with time. This conclusion was based on the fact that about 80 to 85 percent, or about four of every five persons with past penicillin reactions, have negative skin test results. Only a portion, or about one of every five persons with past penicillin allergy gave positive test results, indicating a lingering sensitivity to penicillin.

The survey also studied persons who *never* had a penicillin reaction. Interestingly, it was found that among this group, about one in 15 had positive skin tests. This means that among persons who have no reason to suspect penicillin allergy, a few will have a reaction when treated with penicillin.

Statistics are fine for an overview, but they do not answer the practical question, "How can you tell if a specific patient will or will not have an allergic reaction to a dose of penicillin?"

Only the "major" penicillin antigen is licensed for use in skin testing. However, as penicillin is broken down by the body, other "minor" penicillin antigens are formed that can cause even more serious allergic reactions. At present, there is no way to test for sensitivities to these minor penicillin antigens.

To remedy the situation, the National Institute of Allergy and Infectious

Diseases has begun a multicenter study of the usefulness of skin testing with several penicillin antigens for the prediction of immediate penicillin allergy.

In addition to the "major" antigen, three "minor" penicillin antigens are also being tested. Ultimately, data will be collected from several thousand patients over a two year period. The study is being conducted in eight medical centers. Adult hospitalized patients who need penicillin or one or more of the five other penicillin-like drugs (ampicillin, amoxicillin, carbenicillin, phenoxyethylpenicillin, or phenoxymethylpenicillin) will be asked if they wish to be skin tested for sensitivity to the major and minor penicillin antigens.

If such patients wish to join the study, normal informed consent procedures are followed. However, certain groups of patients, including persons with severe heart, blood vessel, or respiratory problems, patients with unstable physical conditions, patients with extensive burns or rashes, and pregnant women, would not be considered.

The study protocol consists of three simple phases: 1) asking the patient if he or she has ever had a reaction to penicillin, 2) standardized procedures for skin testing and recording results, and 3) careful observation of patients who must receive penicillin to treat bacterial infections.

The test procedure itself introduces a very small amount of antigen into the skin, about one million times *less* than the average therapeutic dose of penicillin.

Skin test results will be used to make treatment decisions. Persons negative to all four test antigens are referred to their doctors for needed treatment with penicillin or penicillin-like drugs. In contrast, persons who are positive to one or more of the skin test antigens would not be so treated but would be given a different type of antibiotic.

However, there are certain serious conditions (for example, endocarditis caused by *Streptococcus viridans* and life-threatening infections caused by pseudomonas or serratia bacteria) for which penicillin is clearly the most effective treatment. Persons with these infections who show positive skin tests to any of the four antigens would have to be treated with penicillin, but only after a careful desensitization procedure. In several reported studies, such desensitization approaches have been very successful in controlling the infection and in avoiding anaphylactic reactions to penicillin.

It must be emphasized that skin testing for penicillin allergy should not be done on a person who has no immediate need for the drug but who "just wants to know." There is ample evidence that the status of a person's sensitivity to penicillin changes with time. The only valid use of penicillin skin testing is for a person who has a definite medical need for penicillin or closely related drugs.

If it can be shown that skin testing with the complete set of penicillin antigens can accurately predict who may safety be treated with penicillin, then the study may lead to the licensing of the minor antigens as skin test materials. The four penicillin test antigens are also the first complete set of drug antigens ever produced and tested. The knowledge gained from the study will be very valuable and may encourage development of complete sets of test antigens for other common drugs. ■

Heavy Drinking Can Cause Impotency . . . Sterility

Prepared by Research Resources Information Center

Many men may be making themselves impotent, sterile, and more feminized by chronic alcohol abuse, according to a recent report by the Division of Research Resources of the National Institutes of Health.

While it is difficult to identify the amount of alcohol consumed that will cause sexual function loss, Dr. David Van Thiel, associate professor of medicine at the School of Medicine, University of Pittsburgh, is certain that these problems are not restricted to skid row or end-stage alcoholics. The early signs of alcohol damage to the reproductive system can appear after a single binge.

Studies conducted at NIH's General Clinical Research Center (GCRC) of the Presbyterian-University Hospital in Pittsburgh show that drinking enough alcohol to cause a hangover can decrease testosterone levels in normal, healthy men who may be occasional drinkers. Dr. Van Thiel finds symptoms of alcohol abuse in many young men complaining of infertility.

About 9 million adult Americans are alcoholics, and about 95 percent of these people are employed. They are obviously not ostracized or debilitated because of their alcohol abuse, but sexual dysfunction is a major problem for many of them. A good percentage of them begin having sexual problems while they are comparatively young.

Dr. Van Thiel suggests that five to eight years of drinking an average of a pint or more of hard liquor a day may cause loss of sexual function entirely. Seventy to eighty percent of male alcoholics suffer decreased libido, impotence, and sterility. These effects of chronic drinking may persist between intervals of drinking and possibly even after an alcoholic completely stops drinking. Although many men may regain some sexual function if they stop consuming alcohol, for some, the damage may be irreversible.

Dr. Van Thiel and his collaborators believe they have determined in part the method by which alcohol upsets normal sexual function. Scientists had thought that sexual dysfunction resulted indirectly from alcohol-induced liver damage, but, according to Dr. Van Thiel's 6-year study, alcohol directly damages the gonads and parts of the brain.

Specifically, it seems to damage sections of the hypothalamus and pituitary that control the function of the testes.

The hypothalamus releases gonadotropin-releasing hormone (GnRH), which in the pituitary stimulates the release of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In males, these hormones stimulate the testes to produce testosterone and sperm, respectively.

The Pittsburgh GCRC researchers found that some male alcoholics have low testosterone levels. In addition, they have decreased levels of gonadotropins (LH and FSH) compared to values that would be expected, considering their low testosterone levels. Low testosterone levels should stimulate increased levels of GnRH and gonadotropins, but that does not occur in these men. The researchers have evidence that the decreased levels of gonadotropins are due to damage to the part of the hypothalamus that produced GnRH.

But the effects of alcohol on the brain's control of sexual function are less important than alcohol's injury to the testes, according to Dr. Van Thiel. He reasons that alcohol is a gonadal toxin directly damaging Leydig cells, which produce testosterone, and sperm. This damage to the testes is independent of the brain injury.

Their low sperm counts make these men sterile and their low testosterone levels may make them impotent and decrease their sex drive.

Chronic alcohol abuse also makes some men appear more feminine. Alcoholic men may exhibit changes in secondary sex characteristics, such as redistribution of hair and fat to patterns more like those of females. The Pittsburgh investigators have described a biochemical mechanism by which this occurs: a combination of reduced testosterone levels and increased estrogen levels. Estrogens are excessive in alcoholic men because of the increased peripheral conversion of weak adrenal androgens to compounds with estrogen activity. Dr. Van Thiel has determined that alcoholic men have increased estrogen levels in peripheral cells—for example, in their breasts.

One of the most important aspects of the study, he believes, is that infertility caused by alcoholic abuse can now be diagnosed early. No extensive tests are necessary; questioning the patient should reveal the cause.

If infertility due to alcohol can be diagnosed early, sexual functions may improve. Regardless of the extent of damage, the best treatment for the problem, according to Dr. Van Thiel, is to stop drinking. There is no other current therapy of proved value. He believes the effects of alcohol on sexuality may be additional persuasive evidence for patient education in the prevention of alcohol abuse.

The studies in Pittsburgh were supported by the National Institute on Alcohol Abuse and Alcoholism, the Distilled Spirits Council of the United States, Inc., and the General Clinical Research Centers Program of the Division of Research Resources, NIH.

For further information on the study, write to Dr. David Van Thiel, University of Pittsburgh, School of Medicine, Scaise Hall, Room 100-J, Pittsburgh, PA 15261. ■

Vitamin E Protects Against Cell Damage Caused By Genetic Disorders

by Susan Johnson

Large doses of vitamin E can protect against white blood cell damage and/or anemia in patients with certain genetic disorders in which glutathione metabolism is defective, studies at NIH and other research centers have shown. The vitamin does this without correcting the underlying defect.

Glutathione, a substance found in most body tissues, protects polymorphonuclear leukocytes (PMN's) and red blood cells from damage by oxidizing agents. These agents harm cells by reacting with their membranes and enzymes, thereby impairing the function of these vital cellular components.

PMN's are white blood cells that defend the body against infection by engulfing and killing bacteria and other microorganisms. During this process, the PMN releases several times the normal amount of hydrogen peroxide, an oxidizing agent instrumental in killing bacteria.

While hydrogen peroxide destroys foreign organisms, it can also harm the cell itself if allowed to accumulate. Glutathione reacts with excess hydrogen peroxide and reduces it to harmless compounds.

PMN's deficient in glutathione cannot deactivate excess hydrogen peroxide, and as a result suffer debilitating damage to their membranes and other components. The ability of these cells to kill bacteria is greatly reduced, possibly leaving the patient more vulnerable to infection.

Red blood cells are exposed to many oxidizing agents during their 120-day lifespan. Glutathione provides a major defense against damage by these agents. A deficiency of glutathione can lead to destruction of red blood cells, which results in anemia, a shortage of red cells in the blood.

In a study conducted at the National Institute of Child Health and Human Development, investigators gave vitamin E to a 2-year-old boy born with an enzyme deficiency which prevented him from making sufficient amounts of glutathione. The boy was anemic, and the ability of his PMN's to kill bacteria and other microorganisms was impaired. Since taking vitamin E, his red blood cell survival has improved and his PMN function has been normal for 18 months.

The boy's younger brother was born with the same disorder, called glutathione synthetase deficiency. Vitamin E therapy was initiated when he was 4 days old. This infant has had normal PMN function and his red blood cell survival has been normal for the past year.

The protection afforded by vitamin E presumably stems from its property as a powerful antioxidant, the investigators explained. The vitamin neutralizes oxidizing agents before they can attack cellular components. It does not correct the metabolic deficiency in the cell.

In another glutathione-related disorder, called glutathione reductase deficiency, patients produce insufficient amounts of an enzyme needed to reduce glutathione. Glutathione must be in the chemically reduced state to inactive oxidizing agents. Vitamin E can protect against damage to PMN's in patients with this defect, Dr. Dirk Roos, Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, told an audience at NIH recently. Whether or not the vitamin can protect against red blood cell destruction in these patients is unknown.

Both of the disorders discussed above are rare. A third glutathione-related disorder, glucose-6-phosphate dehydrogenase (G6PD) deficiency, is perhaps the most prevalent of all genetic defects.

In this disease, which occurs in several forms, an enzyme needed to keep glutathione in the reduced state is lacking. The disease is characterized by red blood cell destruction; PMN damage is rarely a problem.

Patients with the commonest form of the disorder, Mediterranean G6PD deficiency, have mild, chronic anemia. Upon exposure to oxidative drugs or infections, they develop serious, sometimes fatal, acute anemia. Among the drugs that can trigger this response are antimalarial drugs, a class of antibiotics called sulfonamides, and certain analgesics.

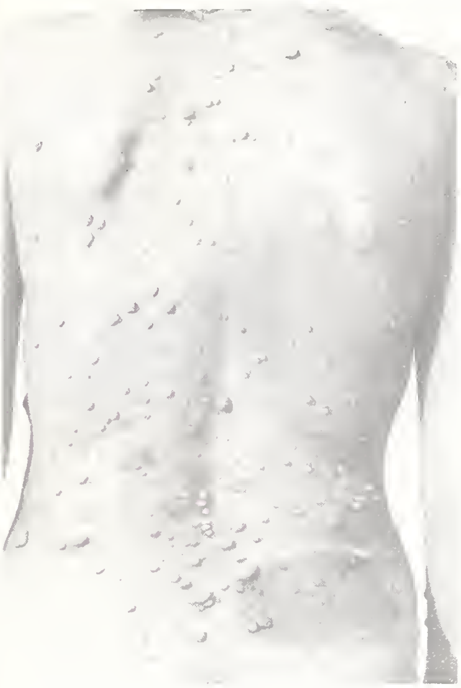
Studies by NIH investigators working in Athens, Greece, have shown that vitamin E significantly reduces the rate of red blood cell destruction in patients with mild anemia from Mediterranean G6PD deficiency. It is not clear whether the protection offered is sufficient to overcome the severe anemia brought on by drugs or infection.

In another, less common, form of G6PD deficiency, patients suffer severe, chronic red blood cell destruction. Large doses of vitamin E do not help most patients with this form of the disease, NICHD studies have shown.

The study of glutathione synthetase deficiency was reported in the *New England Journal of Medicine,* Vol. 301, No. 17 (1979), and the research on Mediterranean G6PD deficiency was reported in the *New England Journal of Medicine,* Vol. 303, No. 8 (1980). Both studies were supported in part by NICHD. ■

Elephant Man's Disease Studied at NIH

by Catherine R. Powell



Hundreds of neurofibromas cover the skin of this patient with NF. The disease is also marked by the presence of "cafe-au-lait" spots, which appear on the lower back of this individual. NIH PHOTO 1669

The curse of the "Elephant Man," the disease dramatized in the current play and movie, afflicts approximately 100,000 Americans—one of every 3,000 live births. The medical name for the disease is Neurofibromatosis (NF), or Von Recklinghausen's disease. It affects both sexes and all ethnic groups equally throughout the world.

Although NF is incurable—its symptoms can often be controlled by careful medical and surgical management.

NF is the most common, clinically severe single gene disorder affecting the central nervous system, exceeding the combined frequencies of Huntington's Disease, Myotonic Dystrophy, Charcot-Marie-Tooth and Duchenne Muscular Dystrophy. NF is also more common than sickle cell disease or cystic fibrosis.

Individual NF victims may be quite disfigured, as was John Merrick, the original Elephant Man. His innumerable skin tumors and cranial and skeletal deformities caused him considerable physical pain as well as the scorn and mistreatment of 19th century London society.

NF signs can be very mild, consisting of a small number of flat, brown birthmarks, called "cafe-au-lait" spots and multiple benign tumors on or under the skin of any part of the body. The disorder may present with only a few spots or tumors or it may progress to hundreds of neurofibromas, some of which can become large and unsightly. Sizeable internal tumors may also develop in the brain, along peripheral, cranial and spinal nerves. Movement, hearing and sight may be impaired as a result. Scoliosis, or curvature of the spine, is a common complication. Approximately 20 percent of NF cases are severe enough to require evaluation or therapy in a hospital setting.

Despite its prevalence and potential severity, little research has been done on NF since it was first named more than 100 years ago by a German pathologist, Fredrich von Recklinghausen.

In June 1979, NIH's National Cancer Institute (NCI), with the National Neurofibromatosis Foundation and Baylor College of Medicine, sponsored a symposium on Biologic Approaches to Neurofibromatosis which will generate the first major publication of research findings on NF in nearly 25 years. The proceedings will be published as a book in early 1981 by Raven Press.

This year, NCI's Clinical Epidemiology Branch has evaluated a number of NF patients in the NIH Inter-Institute Genetics Clinic. Through clinical and laboratory studies, the researchers hope to identify clues to the variability of the disease and its link to cancer.

The clinical researchers are concentrating on certain subgroups: 1) identical or fraternal twins with one or both affected; 2) families with four or more affected individuals alive over two or preferably three generations; 3) families with two or more affected siblings and both parents apparently unaffected; and 4) NF patients with cancer.

The clinicians are also conducting a questionnaire survey of NF patients and their families who are members of the National Neurofibromatosis Foundation. Occurrence of cancer, patterns of clinical expression and transmission, causes of death and patient's psychological response to their disease are being investigated. Preliminary results from the survey show that NF patients are at a higher risk for developing cancer of the nervous system than the normal population.

Scientists know that NF is genetically passed via an autosomal dominant gene. A victim has a 50 percent chance of transmitting the disease to his or her offspring. However, no laboratory or clinical test can as yet predict how severely these children may be affected. For example, an NF patient with relatively few cafe-au-lait spots and pea-sized skin tumors could produce a severely affected child and the opposite is also true.

About half of all NF cases develop as new spontaneous mutations with no previous history in the family. NF is the most common known spontaneous mutation of an autosomal dominant gene. Once such a mutation occurs, the defective gene will be transmitted to 50 percent of the offspring and with the same clinical variability as the heritable form.

By studying genetic markers in blood from members of large NF families, the NIH researchers hope to identify the location of the NF gene on the chromosome map. If a location is known, a variety of techniques could then be useful in understanding the disease process and in developing diagnostic tests for NF.

Physicians have also observed that NF gets much worse during hormonally active periods, i.e. during infancy, puberty, pregnancy and menopause. Ideally, it may be possible that these aggravated growth periods could therefore be controlled by manipulating hormone levels.

According to Judith L. Bader, M.D. a pediatric oncologist with NCI's Clinical Epidemiology Branch, the development of a laboratory test for the diagnosis of NF is an urgent clinical priority. At present, the diagnosis is made on purely clinical observations—the number of cafe-au-lait spots and neurofibromas. The development of an accurate, easy lab test would benefit patients with equivocal signs, young children at risk for NF who may not yet have developed sufficient manifestations to make a diagnosis, and pregnant women who might be carrying an affected fetus.

Dr. Bader adds that collaborating scientists at NIH and at Georgetown University are presently examining immune markers in affected and unaffected NF patients to look for potential markers of the disease.

Dr. Bader notes that "segmental NF" cases have been reported, in which the victims have NF signs on only half of the body, or restricted to one area. The "segmental" NF patients reported to date have not had affected offspring. Scientists suspect that this condition results from a mutation that affects the embryo after development has begun and thus impairs only those parts of the body that arise from the mutated cell.

Dr. Bader has recently seen a pair of identical twins in which only one was afflicted with NF. This is an unusual situation because twins are usually identical genetically. This situation may represent either non-expression in the unaffected twin or a very early post-zygotic mutation just after twinning in the affected twin. Normally, both twins would be expected to be the same genetically, unless one twin has a mutation of the NF gene soon after twinning.

The NIH team also hopes to develop, from their clinical observations and the survey, a life-table for NF victims. By establishing life expectancies and comparisons of the cancer risk of NF patients and the general population, they can give NF victims more of the information needed to cope with life.

"I am very sympathetic to the difficulties that the NF patients and their families face," says Dr. Bader. "Most of these people can't find a physician who has seen more than one case of NF. Besides the physical pains and emotional aches of disfigurement, not knowing the outcome for themselves and their children makes life very lonely and terrifying for these people." ■

New Drug Treatment Reported for Rare, Blistering Skin Disease

by William Reinckens

New hope for the treatment of an incurable, debilitating inherited skin disease that causes scarring, deformities and malnutrition; and in some cases, can even shorten a person's life span, was reported recently by NIH-supported scientists at Washington University School of Medicine in St. Louis, MO.

Dr. Eugene Bauer and his colleagues reported that phenytoin (diphenylhydantoin), and anti-convulsant drug, significantly reduces the blistering of skin and mucous membranes that characterizes recessive dystrophic epidermolysis bullosa (RDEB).

Children with RDEB have skin so sensitive to friction, that, in severe cases, everyday actions like rubbing an eye or wearing shoes can raise massive blisters originating in the deepest layers of the skin. Continuous skin destruction and regrowth due to friction between fingers and toes often leads to mitten-like deformities. Internal surfaces such as the mucous membranes of the mouth, throat and esophagus can be involved, sometimes affecting the patient's nutritional status. In addition, there is no proved therapy for RDEB, and death, in some individuals, occurs before the age of thirty.

With Drs. T.W. Cooper, N.B. Easterly and D.R. Tucker, Dr. Bauer gave phenytoin orally to 17 patients at Washington University School of Medicine and Northwestern University Medical School in Chicago. After 15 months of therapy, blisters and sores were significantly reduced in the majority of patients.

Twelve of the 17 patients showed a decrease in blistering of 45 percent or more. Nine of these patients were severely affected with this disease. In addition, there was a good correlation between therapeutic response and blood levels of the drug. When phenytoin was temporarily discontinued, symptoms returned or became more severe.

In addition, the overall side effects of the drug were minimal. Two patients experienced lethargy and dizziness at high doses. However, these side effects subsided with no loss of effectiveness when the doses were reduced.

Although the mechanism behind phenytoin's effectiveness in children with RDEB remains unclear, Dr. Bauer and his colleagues found some evidence that it acts by blocking the production and/or release of collagenase, an enzyme that breaks down the protein framework of skin.

This finding reinforces recent data that suggest that the disorder results from the excessive synthesis and accumulation of the enzyme (collagenase), which is found in abnormally high levels in RDEB blisters.

The research was supported by grants from the National Institute of Arthritis, Metabolism and Digestive Diseases, the Division of Research Resources and the National Foundation of the March of Dimes.

The complete report of this research was published in the October 2 issues of *The New England Journal of Medicine.* ■

Diabetes Linked With Viruses, the Environment and Genes

by Hilah Thomas

Investigators at the National Institute of Dental Research (NIDR) are accumulating evidence that links the insulin-dependent or juvenile-onset type of diabetes more closely with viral infections, environmental hazards, and genetic predisposition, all of which may be necessary for this disease to develop.

Although insulin-dependent diabetes accounts for only some 10 percent of diabetes cases, these patients are usually children or young adults whose entire lives depend upon their adjustments to taking insulin daily. Understanding the cause(s) of this disease may ultimately lead to prevention.

Recent research from NIDR has shown that at least one case of juvenile-onset diabetes was caused by a virus, namely Coxsackie virus, type B4. The virus was recovered from the pancreas of a child who died with acute diabetes. After injecting viral material into mice that are particularly susceptible to diabetes, they too developed the disease. Proof that the virus actually was responsible for the diabetes was obtained by coupling a dye to antibody made against Coxsackie virus and showing that this antibody attached to beta cells within the pancreas of the diabetic but not the control mice. Normally, the Coxsackie virus causes only mild, transient respiratory symptoms.

Now, NIDR virologists and their associates have examined pancreatic samples from 250 children who died as the result of 14 different viral infections and report that, in 28 cases, the insulin-making beta cells in the pancreas were damaged in varying degrees. These children were victims of Coxsackie virus, type B cytomegalovirus, varicella zoster (shingles), and congenital rubella or German measles virus.

The pathologists noted that pancreatic tissues of victims of several other viruses appeared to be normal. They observed the greatest destruction of beta cells among children with Coxsackie virus. Damage in the cases of cytomegalovirus and varicella zoster was less severe, and some children with each of these viral infections had undamaged pancreatic tissues.

The scientists concluded that whereas more than one virus may damage insulin-producing cells in the pancreas, many

Dr. Takashi Onodera, a Visiting Associate from Japan, is using a double-labeled immunofluorescence antibody technique to study viral-induced diabetes.
NIH PHOTO 1670

potentially damaging viral infections apparently have no overt diabetic consequences. An explanation for this difference has come from animal research in their laboratory.

Some strains of mice are known to develop diabetes after infection with certain viruses (e.g., encephalomyocarditis virus), whereas other strains recover from the same infection without residual diabetes. This capacity of mice to develop virus-induced diabetes has been shown to be genetically-controlled. That is, only animals with the right genetic background develop diabetes when exposed to a virus.

In man, a tendency towards diabetes also seems to run in certain families. But even in these families, some individuals escape diabetes, while in other families with no known genetic flaw, some members succumb to the disease.

The NIDR investigators then tested a theory that several environmental insults contribute to diabetes. Streptozotocin, a drug used to induce diabetes in experimental animals, when given in fairly large doses, produces diabetes by selectively killing beta cells. However, the scientists experimented with low doses which destroyed some beta cells, but not enough to produce diabetes.

Mice given streptozotocin were then infected with virus. Under these conditions encephalomyocarditis virus caused diabetes not only in the genetically-susceptible strains of mice, but also in some of the otherwise resistant strains. The scientists also found that other viruses (Coxsackie viruses, types B3 and B5), which usually failed to produce diabetes in mice, caused diabetes in animals when the reserves of beta cells had been reduced by streptozotocin.

The researchers speculate that cumulative environmental injuries from viruses, chemicals, or toxins, each producing some beta cell damage, finally result in overt diabetes when the beta cell population of the individual has been sufficiently depleted. They now hope to use streptozotocin on laboratory animals to identify other viruses potentially able to cause insulin-dependent diabetes.

A.B. Jenson, M.D., now at Georgetown University School of Medicine, H.S. Rosenberg, M.D., of the University of Texas Medical School, Houston, and A.L. Notkins, M.D., of NIDR reported the human studies in the August 18 issue of *The Lancet*. The animal research with streptozotocin was published in *Nature*, November 27, 1980, by A. Toniolo, M.D., T. Onodera, Ph.D., J. Yoon, Ph.D., and A.L. Notkins, M.D. ■

Sleep Length Determined By Body Temperature Rhythm — Not By How Long You've Been Awake

by Helen Ou

Researchers report that the length of human sleep is determined by natural body rhythms, especially body temperature. The study revealed that in an environment free of time cues—no clocks, radios, windows, etc., a healthy person with a higher body temperature will sleep longer than a person with a lower body temperature on a self-scheduled routine.

Previous studies on the processes that control sleep duration have not been conclusive. A number of studies have contradicted the assumption that the length of sleep is determined by the length of prior wakefulness. So-called "recovery" sleep after even 10 days of total sleep deprivation rarely exceeded 11 to 16 hours, while both longer and shorter sleep times were seen in subjects not deprived of sleep who lived on a self-scheduled routine. This wide variation in sleep duration has been characterized as random and irregular.

Researchers now conclude that variations in sleep duration occur in a consistent and predictable manner, depending on the circadian (daily) phase of the body temperature rhythm at bedtime, rather than how long a person has been awake.

The researchers conducted sleep experiments involving 12 male subjects, living separately for up to six months in an environment free of time cues. Each subject determined his own free-running, non-24-hour sleep-wake schedule. The duration of sleep for each subject was recorded by a polygraph.

By monitoring these circadian rhythms, the researchers found that body temperature at the time of falling asleep is the best indicator of how long a person will sleep. The data also indicated that the rate of REM (rapid eye movement), sleep accumulation, REM latency (inactivity), bedtime selection, and self-rated alertness assessments were correlated with the body temperature rhythm.

The human body temperature varies on a regular daily cycle. On this basis, the researchers found that when the subjects went to sleep when the body temperature was at its lowest they slept an average of 7.8 hours and woke when their temperature began to rise. When the subjects went to sleep at or after the peak of the temperature cycle, they slept almost twice as long—14.4 hours. They slept through the high temperature phase and woke up during the next upswing of the temperature curve. Length of sleep was primarily dependent on its phase within the temperature cycle, even when the chosen bedtimes followed more than 20 hours of prior wakefulness.

All free-running subjects in the study chose to go to bed at certain phases of the temperature cycle much more frequently than at other stages. The greatest bedtime frequency was just after the low point of the temperature cycle.

The process of sleep also varied with the body temperature. The first 50 minutes of REM sleep were accumulated an average of two hours earlier when sleep began just after the low point of the temperature cycle, as compared with sleep beginning just after the high point of the temperature cycle. REM sleep occurs approximately 90 minutes after the onset of sleep and reoccurs periodically. The variation in REM sleep with the time of day is based on a close relationship between a rhythm in REM sleep and the body temperature rhythm. Both of these rhythms can oscillate together at a period different from the sleep-wake cycle itself.

A reanalysis of published data from other sleep laboratories provided supporting evidence for the link between body temperature, sleep duration and REM sleep. Although not previously recognized, other subjects studied in free-running conditions, whether in caves or in isolation facilities, have shown the same dependence of reported sleep duration on circadian temperature phase.

"These findings have major implications for understanding the timing of human sleep and may also help explain the sleep-wake patterns in shift workers and in certain clinical sleep disorders," concludes Czeisler, one of the sleep researchers from Montefiore Hospital in New York.

The researchers were: Charles A. Czeisler of the Laboratory of Human Chronophysiology at Montefiore Hospital in the Bronx, N.Y., and the Sleep Research Center at Stanford University School of Medicine; Elliot D. Weitzman of Montefiore and the Albert Einstein College of Medicine in the Bronx; Martin C. Moore-EDE of Harvard Medical School in Boston; and Janet C. Zimmerman and Richard S. Knauer of Montefiore Hospital and Medical Center.

This study was funded in part by the National Institutes of Health and was reported in the December 12, 1980 issue of *Science*. ■

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News&Features from NIH

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

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News&Features
from NIH

June 1981

Scientists can now request cell cultures from a repository in New Jersey to help them better understand how cells work, form body organs, become malignant or die. This facility, established in the early seventies, will help scientists answer the existing questions of cellular research.

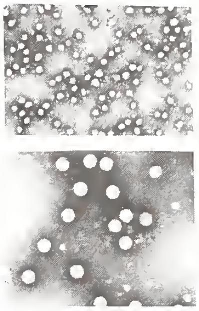
See page 3.

NIH-supported scientists are developing a new dialysis technique which would free patients from kidney dialysis machines. A catheter is implanted in the lining of the patient's abdominal wall, acting as a natural kidney filter. This experimental therapy may allow patients much greater mobility and enable then to carry on a more normal life. See page 8.

Cystic fibrosis researchers are currently working on a new screening procedure that may someday aid young couples with a family history of CF in planning their families. Another test—a more sophisticated one—is being designed to detect carriers as well as victims.

See page 6.

Reye's Syndrome—a childhood disorder that baffles physicians and mimics other illnesses—was the topic of a consensus meeting held at NIH. Medical experts emphasized the importance of early diagnosis and urged parents to learn the signs and symptoms of this life-threatening problem. See page 2.



After several years of testing, researchers have developed a hepatitis B vaccine to protect those individuals whose lifestyles may warrant protection from this virus. The vaccine, which scientists have been working on since the early sixties, is made up of antigens on the surface of the virus. Some experts believe it may be available in less than two years.

See page 13.

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Reye's Syndrome—Meeting at NIH Gives Physicians a New System to Identify Stages

by Ray Fleming

Senator John Melcher (D.-MT), flanked by Drs. Murray Goldstein (right), acting NINCDS director, and Dr. Charles Lowe, Acting Associate Director, Office for Medical Applications of Research study the proceedings of the Reye's Syndrome consensus development conference. NIH PHOTO #1672

The 30th NIH consensus development conference ended on March 4 with general agreement on the criteria for diagnosing and treating Reye's Syndrome and on a series of research recommendations.

Participants at the conference, including research scientists, physicians, parents, and a 13-member panel of experts, discussed in detail the life-threatening disorder that sometimes develops in children and adolescents following a viral infection. The illness results in 10 percent to 25 percent mortality; survivors sometimes suffer permanent brain damage.

Most recently, association with influenza epidemics, has brought Reye's Syndrome, a potentially fatal illness, world-wide attention from the general medical and non-medical public.

Guest speaker Senator John Melcher of Montana called for increased research on Reye's Syndrome, stressed the importance of early diagnosis, and emphasized the need for better public understanding. Remembering families who lost children before the syndrome was clearly defined, Senator Melcher said of the disorder, "It's a heartbreaker, as you know."

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) was the lead agency for the conference, which provided a forum for considering signs, symptoms, and laboratory findings associated with Reye's Syndrome. The effectiveness of different treatments was also discussed, as were the studies needed to further understand and treat the illness.

A comprehensive consensus statement strongly recommended wide distribution of information about Reye's Syndrome. The consensus statement also outlined laboratory tests helpful in diagnosing the illness, and developed a uniform multistage system for measuring the severity of the illness and for guiding treatment. In addition, the statement identified a "lengthening list" of illnesses that mimic Reye's Syndrome and cause diagnostic problems for the physician.

The consensus panel also addressed the question of differing treatments at different stages of the illness. The administration of dextrose-containing fluids was regarded by panel members as a standard therapy for early stages of the syndrome, but several methods used to control the cranial pressure frequently found in later stages were still considered "investigational." Use of intracranial pressure monitoring devices, a subject of considerable interest to conference participants, "has not been shown to have a detrimental effect on outcome in children with Reye's Syndrome," according to the consensus statement.

Panel members urged parents to learn the signs of Reye's Syndrome, and to seek prompt medical attention for their childr if symptoms develop. Specifically, pare should suspect Reye's Syndrome if during or while recovering from a viral illness (most commonly chicken pox or influenza), their children "unexpectedly develop repetitive vomiting and altered behavior such as lethargy, confusion, irritability, or aggressiveness." According to the consensus statement, early diagnosis and intensive pediatric care by an experienced medical team are key factors in improving the survival rate of affected children.

Of the possible relationship between Reye's and the use of salicylates such as aspirin to reduce fever, the panel counseled parents and physicians to "be aware that most, if not all, medications have potential deleterious effects; thus, caution in the use of salicylates in children with influenza and those with varicella is prudent." The panel agreed, however, that more data were necessary before recommending changes in the way physicians treat fever in children.

While emphasizing that complete recovery from Reye's Syndrome could be expected in the majority of cases, panelists also agreed that possible psychological aftereffects might be seen in some children who experience the more severe stages of the illness. For parents, the panel offered useful suggestions to help ease t recovery period.

The consensus statement identified several research areas for greater attention. The cause of the illness was judged to be the most critical research concern, with epidemiology, diagnosis, and disease screening also needing additional study. Treatment, monitoring, evaluation, and follow-up of patients were other areas recommended for future research.

Copies of the final consensus statement can be obtained from Michael J. Bernstein, Director of Communications for the Office for Medical Applications of Research, NIH, Bldg. 1, Rm. 216, Bethesda, Md. 20205 (496-1143). Proceedings of the conference will be available later.

Additional conference sponsors were the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; the National Institute of Child Health and Human Development; the National Institute of Environmental Health Sciences; and the Division of Research Resources. Collaborating agencies were the Centers for Disease Control and the National Center for Health Statistics. Assistance was also provided by the NIH Office for Medical Applications Research. ■

Genetic Cell Repository: A Major Resource—And Still Growing

by Doris Parker

When the culture has "grown" to fill a flask, cells are "harvested" and transferred to ampules for storage until requested for laboratory study.

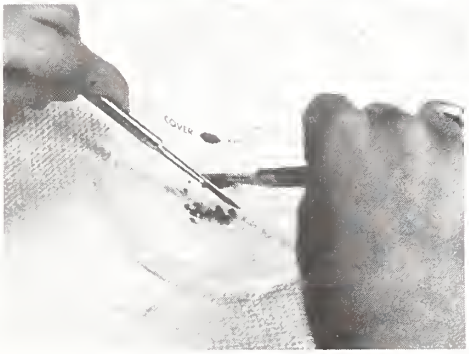
Ampules are heat sealed before being placed for storage in liquid nitrogen tanks at −316°F (−196°C). NIH PHOTO #1673

In a time when commercial companies can "splice genes" for profit, it's hard to remember that just 30 years ago, very little was known about the genetic information packed inside the human cell. Watson and Crick had yet to publish their "double helix" theory about the structure of DNA, the material that comprises our genes. The biochemical "language" in which genetic instructions are "written" was not known. In fact, scientists didn't even have an accurate count of the number of human chromosomes.

Today, research on cells themselves is bringing us tantalizingly close to understanding such key questions as how cells differentiate to form body organs, why some cells become malignant, and why cells eventually age and die. Moreover, developing knowledge holds out the hope that scientists may one day be able to replace disease—producing genes with normal ones—or activate some genes and deactivate others to treat disease.

This explosive research progress has been made possible in large part by the development of techniques for growing human cells in the laboratory—and by greater availability of these cells for scientists who want to study them.

Repositories ("cell banks") now supply many kinds of cells to scientists. As biologist Lewis Thomas has put it, cells have become "neat and handy" laboratory instruments for researchers seeking to understand the cellular and molecular processes underlying health and disease.



Culture of cells from a patient with a genetic disease starts with a small sliver of skin taken from the patient's forearm. Tissue is cut into tiny pieces and added to nutrient solution in a flask, where the skin cells will multiply. NIH PHOTO #1674

The Human Genetic Mutant Cell Repository in Camden, New Jersey—now the largest cell repository in the world—ships more than 3,000 cell cultures a year to scientists in the United States and abroad. The repository, which was established in 1972 under a contract from the National Institute of General Medical Sciences, collects, grows, stores and makes available cell cultures from patients and their families with genetic diseases and chromosomal abnormalities. The repository also contains some cell lines from animal models of human disease and from normal controls.

The repository collection, which now numbers nearly 4,200 specimens, is carefully documented with verified disease diagnoses and family history for each cell line. Cell lines represent a number of diseases that are clearly hereditary (more than 2,000 such diseases have been identified), as well as certain wide-spread disorders in which genetic factors play a less well-defined but important role.

Since each cell in the body contains all of an individual's genes, any defective gene should be present in any type of body cell. The repository contains some cells obtained from blood samples; however most of the cells stored are skin cells, or fibroblasts, which are also easy to obtain—just a tiny sliver of skin from the patient's forearm is all that's needed to start a culture. The samples can be collected by health professionals anywhere, then sealed with a little antibiotic (since skin is not sterile) and sent to Camden.

At the repository the skin sample is cut into tiny pieces, each of which is placed in a culture flask with a "growing medium" containing fetal calf serum. After 3 to 4 weeks in an incubator, the multiplying cells are transferred to additional flasks to continue to grow. When 12 to 15 flasks of the cell line have been accumulated, the cells are harvested in ampules and stored in liquid nitrogen at a temperature of −316°F until requested for research. When properly thawed, these living cells will resume their functions and start to multiply again.

Cells from the Camden repository are being used to study many different disorders, both clearly hereditary conditions such as rare Lesch-Nyhan disease (which causes profound mental retardation) and common disorders such as arthritis and diabetes that may have a genetic component.

At present, the repository is establishing a collection of cell lines from patients with psychiatric disorders, including schizophrenia and manic-depression. This collection will be helpful to investigators trying to understand psychiatric illness from a biochemical point of view.

Hypercholesterolemia is a genetic disorder that causes abnormally high blood cholesterol levels and may account for some 20 percent of all heart attacks in patients under 60. Using cells from the repository, investigators have learned how to identify individuals with this disorder, who are at risk for an early heart attack, allowing them to take preventive measures such as low-fat diets, appropriate medication, and changes in life style.

Often cell biologists discover that their research findings have unexpected relevance for areas outside the focus of a particular project. For example, scientists studying DNA repair have turned their attention to a variety of diseases of nervous system degeneration, including Huntington's disease. The results have led to a hypothesis that a basic defect in these diseases is a decreased ability to repair damaged DNA. Understanding the foundations of such diseases is important, and confirmation of these results could eventually lead to presymptomatic diagnosis of the disease.

Such a test could be particularly important for genetic counseling for families in which Huntington's disease has appeared. Symptoms of this fatal disorder—which causes progressive deterioration of mind and body—most commonly do not appear until its victims reach their thirties or forties. By that time they may have passed the gene along to children, each of whom would have a 50 percent chance of developing the disorder.

Another important area of research involves cells with certain spontaneously occurring abnormalities of the chromosome. One of these, "translocation"—where part of a chromosome has broken off and become stuck to another chromosome—plays an important part in "gene mapping." Gene mapping, locating where and on what chromosome a particular gene lies, is one of the fastest growing areas of genetic research. Determination of the location of defective genes that cause serious illnesses brings the possibility of cure a giant step closer.

Says Lewis Thomas about today's explosion of cellular research, "There are fascinating ideas all over the place, irresistible experiments beyond numbering, all sorts of new ways into the maze of problems."

The next 30 years of unraveling the secrets of the cell should be no less exciting than those just past. ■

Researchers Consider Chemical Exposure a Source of Disease in Children

by Thomas Hawkins

Pediatricians are urged to look into environmental and occupational chemical exposure as a possible source of disease in children. Dr. Walter J. Rogan points out in the *Journal of Pediatrics* (Vol. 97, Nov. 1980, No. 5) that exposure can cause toxicity in the unborn and in young children but may not even cause symptoms in adults. Often children are exposed to chemicals or other toxic substances through specific catastrophic situations such as chemical spills, or from their parents' work clothes, or from the environment.

Dr. Rogan, an epidemiologist in the Biometry Branch of the National Institute of Environmental Health Sciences, (NIEHS) notes that puzzling symptoms, signs, or laboratory abnormalities may be related to chemical exposures, and that physicians should inquire about the occupation and hygiene of all family members. Occupations involving exposures to toxic substances are not uncommon. According to the National Institute of Occupational Safety and Health (NIOSH), there are over 100 jobs involving lead exposure alone. Sometimes children may come in contact with environmental toxins by their mothers' milk. Dr. Rogan notes that, "any highly lipid (fat) soluble chemical with which a woman comes in contact might well appear in her milk."

Everyone, including infants and children, can be exposed to PCBs and DDT. These are passed to the children through breast milk and through water, food, air, and in some cases, bodily contact, the same as an adult.

Pediatricians should be aware that sometimes infants are breastfed at the workplace, causing exposures that are more immediately transmitted in this situation. Dr. Rogan cites an incident where a woman ate lunch with her husband every day in a drycleaning shop. Her exposure to tetrachlorethylene, a drycleaning substance, caused prolonged cholestatic jaundice in her breastfed child, which was resolved once the source of exposure was discovered and breast feeding discontinued.

New, energy efficient homes and older restored homes present potential situations where children might be exposed to toxic substances. New, better insulated, more tightly constructed homes tend to retain carbon monoxide from wood and coal heating systems, as well as fumes given off by fiberboard and other construction materials containing formaldehyde. Restoration of inner city housing reintroduces hazards to children exposed to lead-based paint. The lead reenters the air when old painted surfaces are sanded. Lead has also caused problems in homes where battery casings have been used as fuel for heating.

Other childhood exposures have occurred as the result of catastrophic incidents, such as the TCDD exposure in Seveso, Italy, and the PCB exposure in Yusho, Japan. Here in the United States waste dump sites similar to Love Canal (in New York) pose a long-term challenge to researchers and clinicians, as the health effects of exposures to multiple substances must be discerned.

Dr. Rogan says: "The management of persons exposed to potentially toxic agents can be vexing. The human toxicity to be expected from an agent may be unfamiliar to the clinician or may be unknown. Not all persons exposed may have symptoms, and different symptoms may be seen in different people. When the exposure is a carcinogen, the expected latency period of many years makes diagnosis difficult; finally, the fear of litigation, and testimony may be present."

Nonetheless, since these diseases are among the most preventible, the rewards for maintaining the "high index of suspicion and exploiting research opportunities as they arise is substantial," Dr. Rogan concludes.

NIEHS is the principal federal agency for basic biomedical research on the health effects of environmental agents. Located in Research Triangle Park, North Carolina, it is the only one of the National Institutes of Health not located in Bethesda, Maryland. ■

Researchers Moving Closer to Finding a Better Therapy for Diabetes

by Susan Gerhold

Researchers at the Mayo Clinic in Rochester, Minnesota, supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, recently compared three different approaches to regulating blood glucose levels in diabetics. Their results showed that all three regimens—the closed-loop intravenous insulin infusion, the open-loop subcutaneous system, and the intensified conventional insulin therapy were basically comparable, but with some differences in effectiveness and practicality.

Present modes of therapy have not permitted the diabetic adequate control of glucose because the insulin injections cannot mimic the pancreas and provide enough insulin to control the disorder. Scientists then developed the closed-loop system or the artificial pancreas, since several attempts of pancreatic tissue transplants failed in other studies. Using this system the rate of insulin is controlled by changes in blood sugar. The patient can achieve normal levels of blood glucose but they have higher than normal levels of insulin. The device is also cumbersome, can only be used for short periods of time, and requires continual blood sampling.

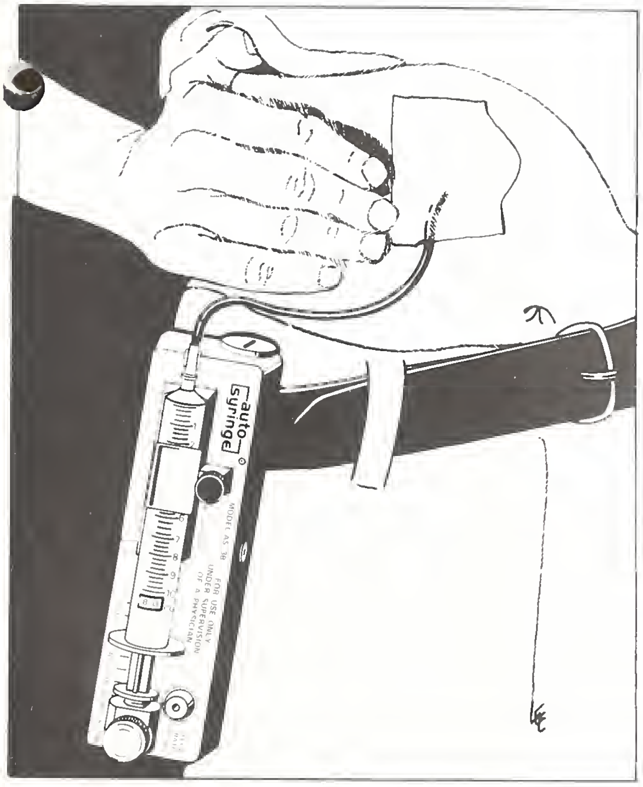
The open-loop system administers a predetermined amount of insulin, based on the patient's previous insulin requirements. This device is portable and allows the patient full freedom of movement. It is actually a small pump which delivers insulin through a catheter to a vein or subcutaneously (beneath the skin tissue).

When using this system the diabetics achieved approximately normal levels of blood glucose, just as they did using the closed-loop system. However, these patients experienced hyperinsulinemia, or an excessive amount of insulin in the blood.

The third regimen—intensified insulin therapy—(multiple subcutaneous injections of insulin) is the least expensive treatment and requires no additional equipment. However, some users require up to four injections daily, making this therapy somewhat inconvenient, and to some patients psychologically unacceptable and difficult to manage. While this method rarely restores glucose to normal levels, the blood glucose levels in this study were comparable to those used in the open and closed-loop system.

Researchers are now better equipped with new tools for achieving and measuring glycemic control. Future studies will include designing smaller, efficient pumps that provide more complex programming of insulin doses, and more sophisticated alarm systems to warn the user of malfunctions—human or mechanical.

This study appeared in a recent issue of the *New England Journal of Medicine.* ■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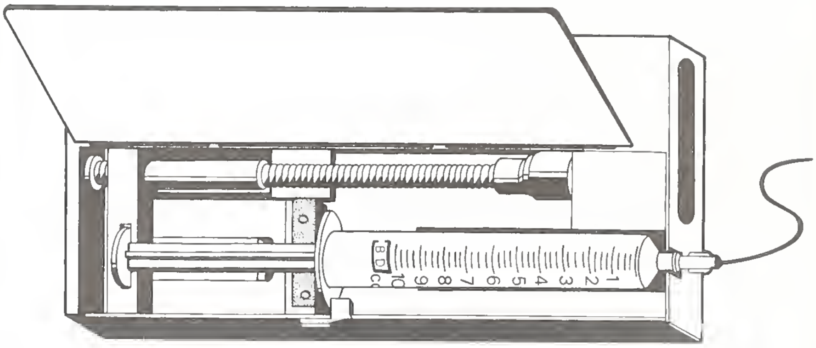
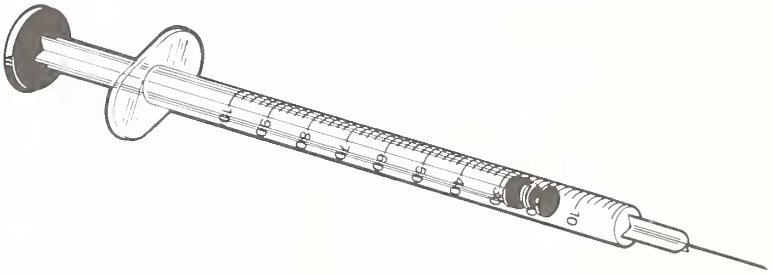
FOR USE ONLY UNDER SUPERVISION OF A PHYSICIAN



The Auto Syringe and the insulin infusion pump are both in experimental stages, however these automatic pumps enable the diabetic to inject appropriate dosages of insulin when needed without using several injections at different sites.



The intensified insulin therapy requires a syringe filled with insulin for daily injections.

Injury Stalks Weekend Drivers

by Ray Fleming

To "steer clear" of excessive weekend driving might well be the warning offered by the National Institutes of Health to millions of American young men between the ages of 15 and 24. According to a newly released survey sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the combination of young males, motor vehicles, and weekend traffic produces a significant number of the severe head injuries in the United States each year.

The National Head and Spinal Cord Injury Survey confirms several long-proposed theories about the occurrence of injuries of this type. The study reveals that the rate of male head injury from all causes is more than twice the rate for females, that 15- to 24-year-old men suffer the most injury, and that traffic accidents cause nearly half of the cases requiring hospital care. Weekends, states the report, are the most dangerous time for injury.

NINCDS scientists believe that the survey provides the first reliable statistical picture of head and spinal cord injury in the United . Citing incidence and cost figures, the study provides valuable information for scientific investigators, physicians, community health-care and public safety planners, and the families of those in high-risk categories.

Report statistics are expected to have an impact on the direction and funding of future research in the area. The information is also likely to be useful in evaluating local emergency facilities and rehabilitation services, and in the hiring and assigning of medical personnel. The survey suggests, for example, that a hospital with only one neurosurgeon should make sure that the physician is available on weekends.

The study estimated that in one year (1974), 422,000 new cases of head injury were reported, and another 10,000 people were admitted to hospitals because of spinal cord damage. In the same year, an estimated 204 out of every 100,000 Americans were hospitalized for the first time as a result of these traumatic injuries. The total number of hospitalized cases occurring between 1970 and 1974—and still needing medical treatment in 1974—was also calculated: 949,000, or a rate of 450 for every 100,000 individuals.

The economic costs of head and spinal cord injuries to the nation were also included in the report. In 1974, such injuries cost Americans an estimated $2.6 billion, or a projected $4.2 billion in 1980 dollars. This yearly figure was based on both direct medical care costs and indirect costs resulting from lost productivity.

Based on the 1974 data, the individual victim of head injury could expect to lose $4,114 to direct and indirect costs in 1980. The loss to victims of spinal cord trauma was projected to be $14,390, a higher figure attributable to the longer hospital stays and greater costs for the treatment and rehabilitation often necessary in this type of injury.

The report also supplied statistics useful in health care planning. A short hospital stay of 3 days or less was common to 55% of head and spinal cord injury patients, with another 20 percent staying 5 to 9 days and 10 percent remaining 20 days or longer. According to the survey, these figures suggest that in one year, over 40,000 patients spent 3 weeks or more in the hospital as a result of these injuries—an enormous utilization of hospital beds and nursing sonnel.

The study was based on an examination of the 1970-1974 records of 247 selected U.S. hospitals. No important differences in injury occurrence were found to exist among racial groups or in different areas of the country.

The survey was edited by Dr. Dallas W. Anderson of NINCDS and Robert L. McLaurin of the University of Cincinnati, and has been issued as a supplement to the November 1980 *Journal of Neurosurgery.* ■

Preliminary Tests in Progress for Cystic Fibrosis Carriers and Victims

by Maureen Miller
(student intern for the News Branch)

Two tests for cystic fibrosis (CF) are currently being developed that may eventually make it possible to identify both asymptomatic carriers of the CF gene and preterm babies with the disease. The complementary tests, supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) of the National Institutes of Health, may eventually be useful in the overall detection and control of this fatal genetic disease.

Cystic fibrosis affects one out of every 1600 to 2500 babies born each year. It is the most fatal genetic disease in Caucasian children in this country, killing many victims before the age of 30. Since CF is a recessive gene trait, infants can inherit the disease only if both of their parents contribute a CF gene. Nevertheless, one in every 20 Americans carries the CF trait.

Cystic fibrosis results in a malfunction of the mucous-producing glands in which an abnormally thick fluid is secreted and clogs the airways of the lungs and bronchial tree, as well as the ducts of the pancreas. Another major symptom is a high salt content in perspiration. Consequently, CF victims suffer from breathing and digestive problems, and an excessive loss of salt when they perspire. At present, there is no known cure for CF.

Cystic fibrosis is usually diagnosed by a sweat test in which a simple measure of salt in the sweat is taken; however, this test cannot screen CF carriers. Dr. Jan L. Breslow and his team at the Children's Hospital Medical Center in Boston are developing an assay involving skin cells based on the theory that the transport of salt across cell membranes is defective CF cells, and if measured, can distingui them from normal cells.

Researchers obtained skin cell samples from 13 normal subjects, eight children with CF, their parents and three unaffected siblings. All cells were grown in a culture and exposed to ouabain, a drug toxic to normal cells. They found that normal skin cells accumulated twice as much sodium when exposed to ouabain as did cells from CF children and their parents. This finding is compatible with past studies where CF cells were discovered to be relatively resistant to ouabain.

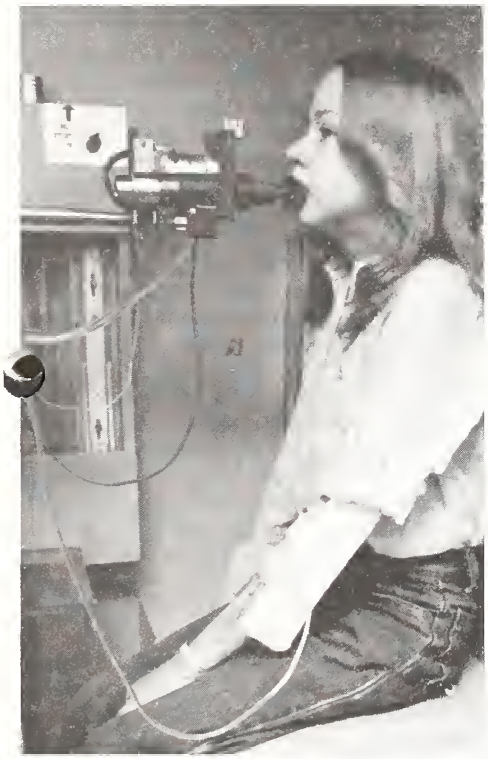
The results of this study strongly suggest that CF carriers can be distinguished from unaffected persons; however, further research in larger populations is needed to confirm the accuracy and reliability of the skin test in detecting carriers.

Should the skin test prove to be an accurate diagnostic tool, CF carriers could be identified, and if they choose, could obtain genetic counseling to determine the probabilities of bearing offspring affected by the disease. Dr. Walter S. Stolz of the NIADDK notes that "the idea of being able to detect a carrier at any time" is a significant advance in genetic counseling for those individuals who know of CF somewhere their family trees.

On the other side of the coin, the function of the intrauterine test is to detect CF in preterm infants via amniocentesis (draw-

A young cystic fibrosis patient is given ultrasonic nebulization treatment, which is an aerosol spray given to the patient before chest physical therapy.
NIH PHOTO #1675

Bronchial drainage or chest physical therapy helps loosen the mucus that builds up in the lungs. The movement or clapping motion moves the thick fluid into larger airways, making breathing a little easier for the CF patient. NIH PHOTO #1677



This cystic fibrosis patient takes a pulmonary function test to measure how well her lungs are functioning.
NIH PHOTO #1676

Vibration physical therapy—a circular motioning of the hands in the chest area, is given to this young patient to clear her lungs. The child exhales while the physical therapy is given and the motion loosens up the mucus, moving the obstruction to larger airways to help the child breathe easier. NIH PHOTO #1678

(All the Cystic Fibrosis photos are compliments of the Cystic Fibrosis Foundation of America)

ing of amniotic fluid from the mother). Dr. Henry L. Nadler and his colleagues at the Children's Memorial Hospital in Chicago are engaged in preliminary studies aimed at developing this test. Saliva and plasma of patients with CF are deficient in certain proteases (enzymes active in digestion). Nadler's studies indicate thus far that amniotic fluid contains MUGB reactive proteases very similar to those in plasma. The investigators project that this abnormal enzyme activity can also be measured in amniotic fluid to identify CF.

To determine a normal control range, investigators obtained 1900 amniotic fluid specimens from second trimester pregnancies, and made quantitative and qualitative measurements of MUGB reactivity via three distinct procedures. Researchers then monitored 13 pregnancies at risk for CF, and compared amniotic fluid from CF risk samples to that of the 1900 control samples. Of the 13 pregnancies, three affected fetuses and 10 normal fetuses were predicted. In each case, the diagnosis was confirmed after delivery by using the sweat test on newborn infants.

These findings suggest that qualitative and quantitative measurements of MUGB reactivity may provide a practical method for prenatal screening of CF. The statistical reliability of each of the three measurement procedures must be upgraded, however. Dr. Nadler cites one example in which the amniotic fluid from a woman with CF revealed abnormal MUGB reactivity in one procedure and normal activity in the other two procedures. At present, then, Nadler notes the "importance of requiring a variety of approaches rather than a single quantitative determination to define the status of the fetus."

Investigators are conducting studies of the effectiveness of the MUGB reactivity test. They will continue to monitor pregnancies at risk for CF as part of this effort. ■

Several Epileptic Drugs Found to Cause Birth Defects in Animal Studies

Prepared by the National Institute of Environmental Health Sciences

Several drugs used to manage epilepsy have recently been found to cause birth defects in animals. Based on this information, physicians are currently advised to evaluate all data on these medications before prescribing them to women of child-bearing age.

Approximately 2 million people in the United States suffer from epilepsy, and the vast majority of these people take medications to control their disorder. In 1857 epilepsy was first treated with bromides. These drugs were used until 1912, when phenobarbitol was introduced. Today, over a dozen different drugs are available. However, a high frequency of birth defects are found in children of mothers taking anticonvulsant drugs such as trimethadione and dimethadione.

Scientists in the Experimental Teratogenesis Section, Laboratory of Reproductive and Developmental Toxicology in the National Institute of Environmental Health Sciences, NIEHS, are currently evaluating the abnormal fetus development and the birth defect potential of chemically related compounds used in the management of epilepsy.

Since epileptic seizures vary, a wide range of drugs are available for the management of this little understood malady. Researchers studied two chemical classes: oxazolidinedione (trimethadione, dimethadione, and paramethadione), all anticonvulsants used in the management of petit mal epilepsy, and succinimide (phensuximide, methsuximide, and ethosuximide) which is used to treat other types of epileptic seizures.

The compounds were injected into mice, were then killed and surgically examined. The uteri were removed and examined for the number of live, dead or resorbing features. Each live fetus was then weighed and examined for internal and external abnormalities.

Results showed that mice given the drug trimethadione, a derivative of oxazolidinedione, suffered abnormalities affecting the skeletal, circulatory, respiratory, genital, and renal systems.

Since women often do not know they are pregnant until several weeks after conception, physicians are urged to prescribe to ALL women of child-bearing age alternative drugs that cause less risk to the early development of the fetus. ■

Kidney Dialysis Patients May Face a Brighter, More Mobile Future

by Jim Fordham

In the future, a growing number of people with kidney failure may be treated using a relatively simple technical innovation known as continuous ambulatory peritoneal dialysis (CAPD). This new and effective dialysis technique allows a much greater degree of freedom for the patient than is possible in other forms of dialysis therapy.

Conventional peritoneal dialysis, from which CAPD evolved, traditionally has been a useful alternative to hemodialysis for removal of body wastes from the blood. The peritoneum is a membrane that surrounds the intestines and other organs in the abdominal cavity. This membrane contains many small blood vessels from which wastes are filtered when dialysate is introduced slowly into the abdomen during the dialysis process.

Peritoneal dialysis does not require the blood to be circulated and purified outside of the body as in hemodialysis. The procedure, in fact, requires no electricity, machinery, blood-thinning drugs, technicians, or other complexities associated with hemodialysis. The wastes that in hemodialysis are filtered from the blood by a machine are instead removed using the thin lining of the patient's own peritoneum as the filtering membrane. In order to make this cavity accessible, a cut is made into the abdomen just below the navel. A permanent catheter is implanted through this small opening in the peritoneal membrane.

CAPD, a portable and potentially less expensive form of peritoneal dialysis developed in recent years, frees the patient from frequent trips to a dialysis center for long, tiring treatment sessions. Patients in CAPD therapy maintain about 2 quarts of dialysis solution in their peritoneal cavities, except for short periods several times during the day, when the dialysis fluid is drained and replaced with fresh solution. CAPD enables patients to walk around, to perform everyday tasks, and even to go to work while their blood is being cleansed.

A patient on CAPD therapy can change his own dialysis solution through use of a small plastic bag that attaches to the tube leading out of the abdominal cavity. Most of the time the bag is empty, and worn neatly folded under the patient's clothing at the waist.

At present, only a small percentage of dialysis patients in the United States use CAPD, but the proportion is likely to increase as the procedure becomes safer and as greater experience reduces the prin-

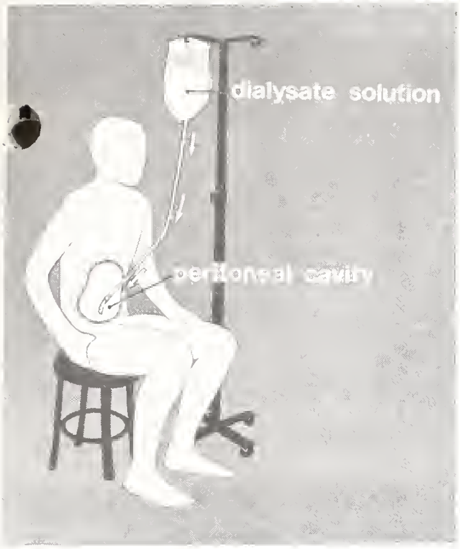


Diagram of continuous ambulatory peritoneal dialysis (CAPD) therapy.
NIH PHOTO #1679

cipal hazard of the therapy, peritonitis (infection of the peritoneum). The risk of peritonitis is reduced when patients are particularly careful in handling the connectors for the bags of fluid.

Despite the proven benefits of CAPD, nephrologists have been concerned that recurrent episodes of peritonitis and constant peritoneal contact with dialysis solutions during this regimen might result in loss of peritoneal permeability, decreasing [illegible] effective clearance of waste products. Recently, however, research contractors of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), Dr. Karl Nolph, of the University of Missouri Medical Center and Dr. Carmelo Giordano, of the University of Naples in Italy, have shown that peritoneal clearance of uremic wastes remains remarkably stable in patients on CAPD, even in the face of episodes of peritonitis. In the majority of cases, CAPD appears capable of permitting effective blood purification for several years, particularly with reduced peritonitis rates. These factors, combined with the potential economies to be realized, make CAPD a promising new approach to maintenance treatment.

NIADDK has supported pioneering efforts in development of this therapy, and continues support of investigations as use of this method of dialysis becomes more widespread across the United States. This research will help define ways to individualize CAPD treatment for patients, and to determine its long-term effects and possible complications, so that a less restricted quality of life is available to many patients afflicted with chronic renal failure.

For further information about CAPD [illegible]tment, patients and their physicians can contact Dr. Karl D. Nolph at the CAPD Information Center, University of Missouri, 807 Stadium Road, Columbia, Missouri 65201. ■

Former Hodgkin's Disease Patients Can Bear Children

prepared by the
National Cancer Institute

Young men and women treated for Hodgkin's disease have a good chance of having children, and their children will probably be normal in growth and development. These were the results of a study performed by oncologists at the National Cancer Institute's Baltimore Cancer Research Program and presented in Washington at the 17th annual meeting of the American Society of Clinical Oncology, April 27-May 3. Philip H. Konits, M.D., said the overall fertility rate was about 50 percent among 81 patients—both men and women—who wanted children. "This is less than the 80 to 85 percent rate for the general population, but much higher than had been thought possible for these patients," he said.

He said also it is not now known whether the lower than normal fertility rate among Hodgkin's disease patients is due to the disease or the therapy.

Dr. Konits and his associates identified the 81 Hodgkin's disease patients who wanted children out of a total of 209 such patients ranging in age from 18 to 45. Thirty-eight were women and 43 were men. A total of 40 patients—23 of the 38 women and the wives of 17 of the 43 men—had 60 pregnancies that resulted in 42 full-term infants, six pregnancies at the time the report was written, two spontaneous abortions, 10 elective abortions, and one set of twins stillborn at 6½ months gestation. The 42 children now range in age from one month to 12 years, with a median age of 4 years. Birth weight, growth, and development were normal. There was one instance of congenital hip displacement, one of pes planus, a foot deformity, and one heart murmur.

There were, however, no differences in the rate of either spontaneous abortions or congenital anomalies compared with the normal population, Dr. Konits said.

More than half the patients—20 women, 22 men—received both chemotherapy and radiation therapy. Thirteen of these 20 women had pregnancies for a fertility rate of 65 percent, while the spouses of only five of these 22 men became pregnant, for a rate of 19 percent. Thirty patients received only radiation therapy, and nine received only chemotherapy.

During laparotomy, an exploratory abdominal operation performed in Hodgkin's disease patients, all the women patients slated to receive radiation therapy had oophoropexy performed on them. In this procedure, the ovaries are lifted and tied to the abdominal wall to remove them from the radiation field. ■

A New Computer System at NIH Gives Users More Options

by Pat Miller

WYLBUR, a computer system used by secretaries, programmers, scientists, and other computer users at NIH has been completely revised. Along with the familiar text editing, users now have additional capabilities for formatting documents, transmitting messages between users, performing computations, and writing computer programs. When WYLBUR was first introduced to NIH, it was used to assist personnel in daily duties such as letter writing, manuscripts, or drafts. WYLBUR is currently used as a convenient way to organize research data, and to create, document, test and maintain computer programs. With this updated version more employees will be able to perform their everyday tasks even more efficiently.

This unique combination of tools was designed and created over the last few years by a group of computer specialists in the Computer Center Branch of the Division of Computer Research and Technology (DCRT). DCRT is responsible for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH.

Originally developed at Stanford University, WYLBUR was first adapted by the NIH Computer Center staff in 1968. The program was made available to users throughout NIH in July 1969 with ten telephone lines. From there, WYLBUR grew steadily, both in usage and system capabilities. Today, WYLBUR has 482 telephone lines and on an average day, over 5,000 people use these lines.

New features and system enhancement have been added regularly over the years to make WYLBUR more useful to the growing number of NIH users. However, it was decided that the system could not support its continued growth or supply the new features that were needed, so a new updated version was designed and implemented.

One of the most important goals for the new version was to maintain as much compatability as possible with the first

The most exciting aspect of the new version of WYLBUR is its ability to perform new functions. Computer technician Carol Kahl demonstrates "document formatting," an improvement that enables the user to automatically arrange written material in columns and various other ways. NIH PHOTO #1680

WYLBUR system in order to assist users in the change. Another challenge was to add to the capability of WYLBUR without unduly affecting the system's simplicity and ease of use.

The increased number of functions make the WYLBUR language much larger. However, many of the new functions are optional; and users may select the particular functions needed for their jobs. This added attraction continues to keep the system simple and easy to learn, and provides users with the opportunity to add optional functions as they become more familiar with the system.

Increased security, system capacity, and operating efficiency are part of the new version. However, to many of its users, the most exciting aspect of this new system is its ability to perform new functions and operations. One of these new functions helps eliminate the accidental loss of data.

The text-handling facilities have been greatly improved. The amount of information that can be stored in working text has been increased.

One major enhancement is the capability of selecting information to be processed. A number of new editing commands have been added and a number of the old editing commands have been improved.

A major improvement was made in document formatting capabilities. The user can arrange line lengths—pre-set with either even or ragged right edges—or can produce text in a multi-column format. Page numbers, headings, indexes, table of contents, and footings can all be incorporated into the text automatically. WYLBUR will automatically generate page numbers. There is also an option for automatically hyphenating words at the end of a line. Document formatting also provides specialized procedures useful in the preparation of scientific or mathematical text.

These features are implemented using "marker commands"—commands that are imbedded within the text, but not printed in the final document. These commands tell WYBUR how to format the document. Marker commands can be used to mark key words and lines, causing them to appear in the index or the table of contents. Document headings and footings are also created using marker commands. Other marker commands can be used to move to a new page, skip a specified number of lines, or specify that a group of lines is to be printed on the same page.

Greater versatility can be achieved through the use of command procedures—a collection of WYLBUR commands and statements that are used to write programs. These commands allow users to tailor WYLBUR to meet their unique applications.

Command procedures may also be used to define new commands, control the order in which commands are executed, ask the user for more information, or perform complex routines involving data manipulation.

WYLBUR still provides access to batch processing services, which enables users to submit a job that will be processed by the computers located at the central facility. WYLBUR can be used to enter the data, to examine the job output, or to display and change the status of the job. These features were incorporated in the previous WYLBUR but have been strengthened a improved in this new version.

Several manuals are available to assist new users in learning the new system. The documentation is designed so that users can learn only the portions of the system that apply to them, without being concerned about capabilities that are not of immediate use.

Questions concerning WYLBUR are being answered by the Programmer Assistance and Liaison (PAL) unit. ■

Offspring of Mice: Greater in Number, Smaller in Size—All Because of Artificial Light

by Hugh James Lee

Continuous exposure to different artificial fluorescent lights each produci a unique light spectrum may exert sign cant effects on creatures including people. Artificial light sources, particularly fluorescent lights which have a markedly different energy spectra from natural sunlight, have been identified by various investigators as having a number of unwanted side effects. Researchers in the Laboratory of Environmental Biophysics at the National Institute of Environmental Health Sciences (NIEHS), have explored the effects on mice of fluorescent light of three distinct colors: daylight simulating (DS), cool white (CW) and pink (PK). "We do not mean to imply by this work that the human effects might be the same as for mice," Dr. Colin Chignell, Chief of the Laboratory of Biophysics at NIEHS, said. "But our results in controlled experiments with mice enable us to learn more about the subtle relationships between certain light conditions and biological processes. Eventually we may learn enough to identify and measure related though perhaps somewhat different kinds of effects on people."

In the NIEHS study, mice were exposed 12 hours per day for 19 months in temperature and humidity controlled cages. The researchers made several observations, namely: the first litter w significantly delayed in both the CW a PK groups compared to those exposed to daylight simulating light; females housed under the cool white light produced litters containing fewer pups than daylight simulating exposed females, while females in the pink light group had more litters than the DS group.

"Mice exposed to the cool white light gave birth to a smaller total number of pups than those kept under the daylight simulating fluorescent lights," Dr. Chignell says.

The light experiment was conducted using C_3H mice, a strain in which the females naturally develop mammary tumors after a certain age. The research found that females kept under the daylight simulating light developed tumors 5.5 weeks later than those kept under the cool white lights and 3 weeks later than those under pink lights.

The differences observed in both the time of tumor development and the differences in reproduction are, according to the NIEHS scientists, attributable to the differences in light spectral energy distributed by the three lighting systems.

The paper reporting the work, titled "The Effect of Different Types of Fluorescent Lighting on the Growth, Reproduction and Lifespan of the C_3H Mouse," is scheduled to appear in a future issue of *Photobiology and Photochemistry.*

Dr. Chignell says he would like to conduct another series of experiments using the same light sources but a different strain of mice to examine whether the different light spectra might produce changes in development or behavior.

NIEHS is the principal federal agency for basic biomedical research on the health effects of environmental agents. Located in Research Triangle Park, North Carolina, it is the only one of the National Institutes of Health not located in Bethesda, Maryland. The Laboratory of Environmental Biophysics at NIEHS examines physical factors in the environment—including noise, light, and microwaves—as they relate to health. ■

Researchers Continue to Look for Plants That May Help Combat Cancer

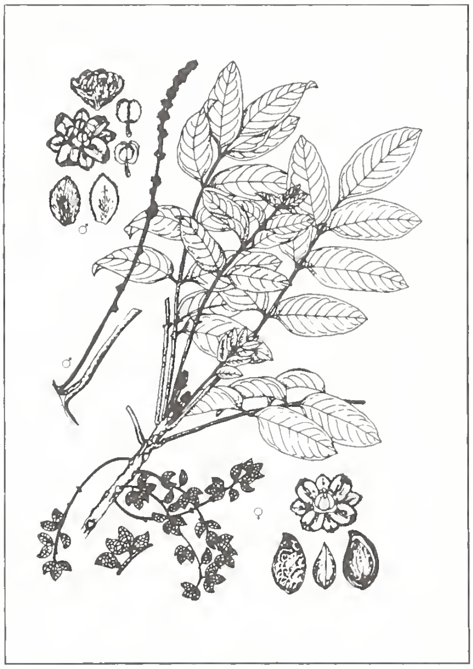
by Esther Solomon

Collecting herbal medicine in primitive African villages may seem an unlikely way to discover new drugs to use against cancer. At the National Cancer Institute (NCI), scientists coordinate a program to test over 5,000 extracts a year from about 2,000 plant samples for anti-cancer activity. A wide variety of plants are collected, including those used in folk medicine.

U.S. Department of Agriculture (USDA) botanists and suppliers from over 60 countries in Asia, South America and Africa, who work under contract to NCI, have collected 30,000 plant species since the program began in 1957. At any time 500 to 1,000 plant samples are in shipment from various parts of the world to USDA.

"We are not likely to develop a wonder drug to cure all types of cancer," Dr. Matthew Suffness, chief of the Plant and Animal Products Section at NCI says, "Cancer is over a hundred diseases, each with its own growth and metabolism characteristics and its own responses to drugs. We are looking for new drugs that will be very effective against certain kinds of cancer."

Dr. Matthew Suffness, chief of the Plant and Animal Products Section, NCI, coordinates the program to test plant samples to anti-cancer activity.
NIH PHOTO #1681



Brucea antidysenterica Mill — The source of the drug bruceantin, is found in this small tree that is found in the highlands of tropical Africa and only abundant in Ethiopia. The active agent is concentrated in the stembark.

Plants have been used to treat cancer and other diseases since prehistoric times. Some of these early folk medicines led to the development of many useful drugs. The root of the Rauwolfia tree, used for centuries by folkhealers in India and Africa to treat insanity, resulted in the discovery of Reserpine, used for high blood pressure.

Feverish children in Ecuador are often given a beverage made from the bark of the cinchona tree. Quinine, a soluble salt extracted from the "fever bark tree" was the first drug found effective to treat malaria.

"We follow up folk medicine leads where we can, but it's a difficult thing on which to base a program," says Dr. Suffness. "Drawings of accurate descriptions are rarely available. The remedy may be an extremely complex mixture of 30 to 60 plants and often the ingredients are secret. Without modern diagnostic methods, there is no way to know which diseases the substance actually was used for."

Jonathan Hartwell, who headed NCI's plant program from 1956 to 1976, reviewed over 3,000 plant species used in folk medicine to treat cancer. One of these was the root of the Mayapple, used by the Penobscot Indians in Maine to treat what was believed to be some form of cancer. The Mayapple root was also recommended for cancerous tumors in an American medical book published in 1849. Today, two semi-synthetic derivatives of the Mayapple, VM-16 and VP-16 (Etoposide), are showing positive results in leukemia and brain tumors.

Two major cancer drugs come from the white and rose-flowered Madagascar periwinkle, used in folk medicine for many maladies including dysentery and toothache. Vinblastine is used to treat Hodgkin's disease and testicular cancer, and Vincristine is an effective treatment for childhood leukemia and Wilms' tumor (a childhood cancer of the kidneys).

In the late 1960's, USDA botanists working in Ethiopia collected samples of an abundant small plant called Brucea. Several years of research with this plant led to the development of Bruceantin, a drug now in clinical trials.

Scientists needed more Bruceantin for tests, but U.S. botanists were not permitted to enter Ethiopia to gather Brucea. A worldwide search for Brucea or related species proved difficult because plant classification systems and names of plants vary widely from area to area, even within the same country.

Brucea grows in Kenya and Tanzania, but is scarce. However, 5,000 pounds of Brucea were collected from Kenya and Tanzania in 1980. A related plant found in Ghana is also too scarce to collect. Chemists studying a species from Indonesia found that it contained different compounds than Brucea which they are working to modify to produce synthetic Bruceantin. Botanists in India and Nepal are looking for a species native to the Himalayas which showed anti-cancer activity when a small sample was tested several years ago.

To produce an experimental drug called Homoharringtonine, scientists use the seeds of an evergreen native in mainland China. After USDA chemists discovered the drug 10 years ago, they were unable to get more seeds. Attempts to cultivate the slow-growing plant in Oregon failed to provide enough material for tests. Researchers tried to obtain the plant from Japan but two years of drought resulted in bad crops, and insufficient quantities of the seed for tests. The Chinese, meanwhile, tested the drug in leukemia patients and reported good results. Recently, China agreed to sell us the pure compound and NCI-sponsored clinical trials will soon begin.

Often a drug which takes years to develop and looks very promising in animal tests proves disappointing in human clinical trials. Such is the case with Maytansine, which took eight years to develop.

In 1976, 31,000 pounds of the Maytenus plant were collected from Kenya and the pure drug was isolated at a cost to NCI of about $650,000. This yielded about 15 grams of Maytansine, enough to treat several thousand patients.

From animal data, it was expected that Maytansine would be most useful against leukemia. As an experimental drug, it was tested only on patients who had not responded to proven therapy.

"Although initial test results were disappointing, Maytansine may be effective on previously untreated patients. It's really an ethical question," Suffness explains. "If you've got a patient with cancer, you've got to give that patient the best available therapy. When we have therapies with four or five drug combinations that are pretty effective with a high percentage of remissions, we cannot justify using an experimental agent for the initial treatment for these patients."

In China, investigators are testing a drug called Camptothecin. Developed under the NCI program, it was dropped from clinical trials in the U.S. when it failed to show activity in patients who had not responded to proven cancer therapies. The Chinese are reporting good results for previously untreated patients.

It can take three to ten years from the time chemists receive a bunch of leaves, stems and other plant parts to the time an active compound is isolated and tested in animals. Crude plant extracts are prepared which contain thousands of chemical components. A slow, painstaking series of complex chemical procedures separate, purify and concentrate the active materials. When a step in the process destroys the anti-cancer activity, the compound is retested at an earlier stage to recover the active components of the mixture. The pure materials are tested against different mouse tumor systems and those which look promising are tested in mice for toxicity before they are approved for limited trials in humans.

Plants which appear negative are often retested since chemical components in plants vary from season to season and from area to area due to different soil conditions and different climates. The plant may contain active materials only during one season or only if it grows in a specific area.

"It's a trade-off," says Suffness. "We don't want to keep testing indefinitely plants that are negative; on the other hand, we don't want to miss something by not testing it at the right location or in the right season."

To test plant extracts, scientists use animal tumors which show the highest predictability for anti-cancer activity in humans, but any animal test cannot be completely accurate for people. Investigators in NCI's Division of Cancer Treatment are now screening new materials against human tumors in "nude mice." These hairless animals have no immune system and do not reject foreign tissue. Although the tumors are not the same as spontaneous tumors in humans, scientists hope they will more accurately predict which extracts will work against human cancer.

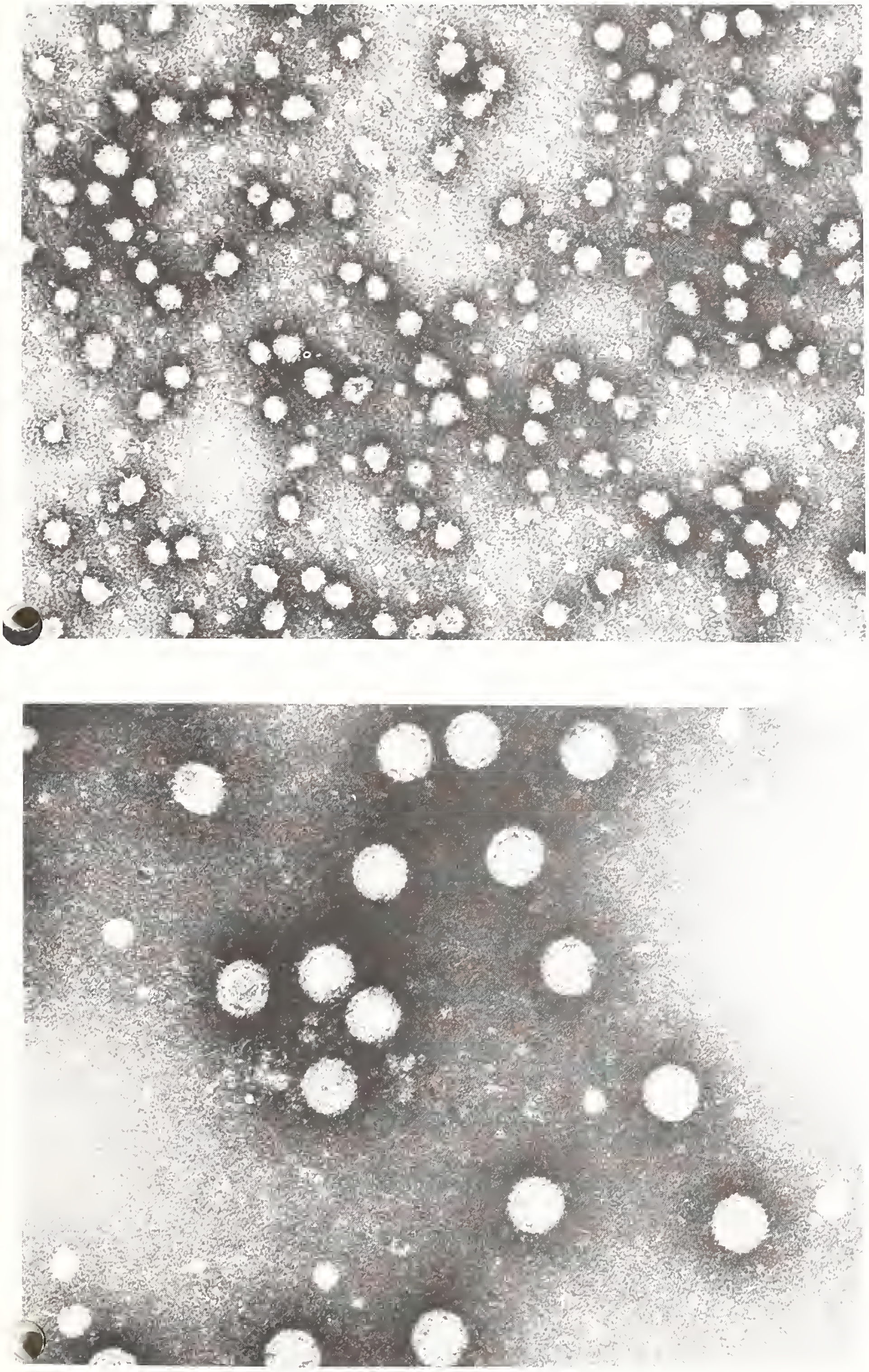
When a drug is chosen for extensive clinical trials, large collections are ma and the drug purification process is modified to produce the compound in large quantities. This process is time consuming and costly.

Currently, six compounds from plants are under development for clinical trials. Although about a hundred extracts enter testing every week, only about one of every 2,000 becomes a candidate for clinical evaluation.

The NCI also tests unsolicited plant products from scientists all over the world as well as previously untested folk medicine mixtures whose components have been identified. "You never know where a good lead might come from," Suffness comments. "We don't want to lose anything just because it sounds a little strange." ■

Researchers Discover Another Vaccine—This Time for Hepatitis B

prepared by the National Heart,
Lung, and Blood Institute



The hepatitis B vaccine is made from inactivated antigens on the surface of the virus, which is shown in the above photos, taken under electron magnification. NIH PHOTO #1682

The discovery of a long-sought, effective vaccine against type B hepatitis recently was announced by the New York Blood Center after a 2-year clinical trial co-sponsored by the National Heart, Lung, and Blood Institute and Merck Sharpe & Dohme Research Laboratories. The vaccine proved better than the developers expected, affording nearly total protection with few side effects.

The type B hepatitis virus is one of the agents that cause acute viral hepatitis. Type B hepatitis was formerly called serum hepatitis because it is frequently transmitted through blood transfusions. In addition, it may lead to chronic hepatitis and cirrhosis, and has been implicated in a form of liver cancer. The type B virus is present in blood of infected individuals, but it can also be spread through breast milk, saliva, and semen. Estimates of the number of cases of type B hepatitis in the U.S. each year range from 80,000 to 150,000. An additional 800,000 people are termed "carriers," able to transmit the disease but who themselves do not have active hepatitis. Between one and two percent of those developing the disease die from it. Many of them already are weakened from illness and acquire the disease through transfusion of blood.

The idea of a vaccine against type B hepatitis was thought of as early as 1964, when researchers found immunologically similar particles in the blood of an Australian aborigine and in type B hepatitis patients. The particles proved to be type B hepatitis surface antigen, and it was suggested then that these antigens could be used as the basis of a vaccine. Shortly thereafter, other workers obtained blood containing the surface antigen, diluted it, heated it to inactivate any infectious virus, and injected the resulting preparation into children who were living in a facility for the mentally retarded. In spite of the extremely high incidence of type B hepatitis in the facility, some of the children receiving the vaccine did not contract the disease.

Attempts to produce the vaccine in a more purified form and in commercial quantities were difficult; type B hepatitis virus could not be grown in the laboratory. The vaccine used in the present clinical study requires more than a year to produce and test. Preparations of the vaccine involves collection of pooled blood, separation of the proteins from the blood and then the type B hepatitis antigen from the proteins, purification and inactivation of the antigen, and a six-month waiting period to see whether chimpanzees injected with the vaccine have any evidence of infection.

Dr. Wolf Szmuness, an epidemiologist at the New York Blood Center, has now conducted a clinical study, involving 1,083 male homosexuals. Male homosexuals, as a group, have an incidence of type B hepatitis that is more than 10 times that of the general population. More than 13,000 volunteers were screened to select the study group, which had to consist of men who had neither type B hepatitis antigen nor antibody in their blood.

The volunteers were assigned to one of two groups. The study group received the hepatitis vaccine at the beginning of the study, a second injection one month later, and a third and final injection six months after the study began. The control group received placebo (blank) injections at the same time intervals. The researchers then observed the groups for 18 months after the final injections to compare the incidence of hepatitis.

Of the vaccinated group, 96 percent developed antibodies to type B hepatitis virus. Few side effects to the vaccine were encountered, although the amount of antibodies in the treated group tended to decrease during the month after the final injection. This is an indication that additional booster shots may be needed to maintain maximum levels of protection. During the observation period, 1.4 percent of the vaccinated group developed hepatitis, but none of these volunteers who produced antibodies to type B hepatitis virus developed the disease. In contrast, 18 percent of the control group, who received placebo injections and thus did not form antibodies to the type B virus, contracted type B hepatitis.

Thus, vaccination reduced the incidence of type B hepatitis by more than 92 percent.

Inoculation against type B hepatitis is not practical or necessary for the general population. Those whose lifestyles or occupations place them in greater likeliho of contracting the disease, however, c now be afforded reliable protection.

The newly developed vaccine may be commercially available in less than two years. Efforts continue, meanwhile, to develop simpler and less costly methods of production and to identify other viral agents which are known to cause different forms of hepatitis. ■

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News&Features from NIH

August 1981

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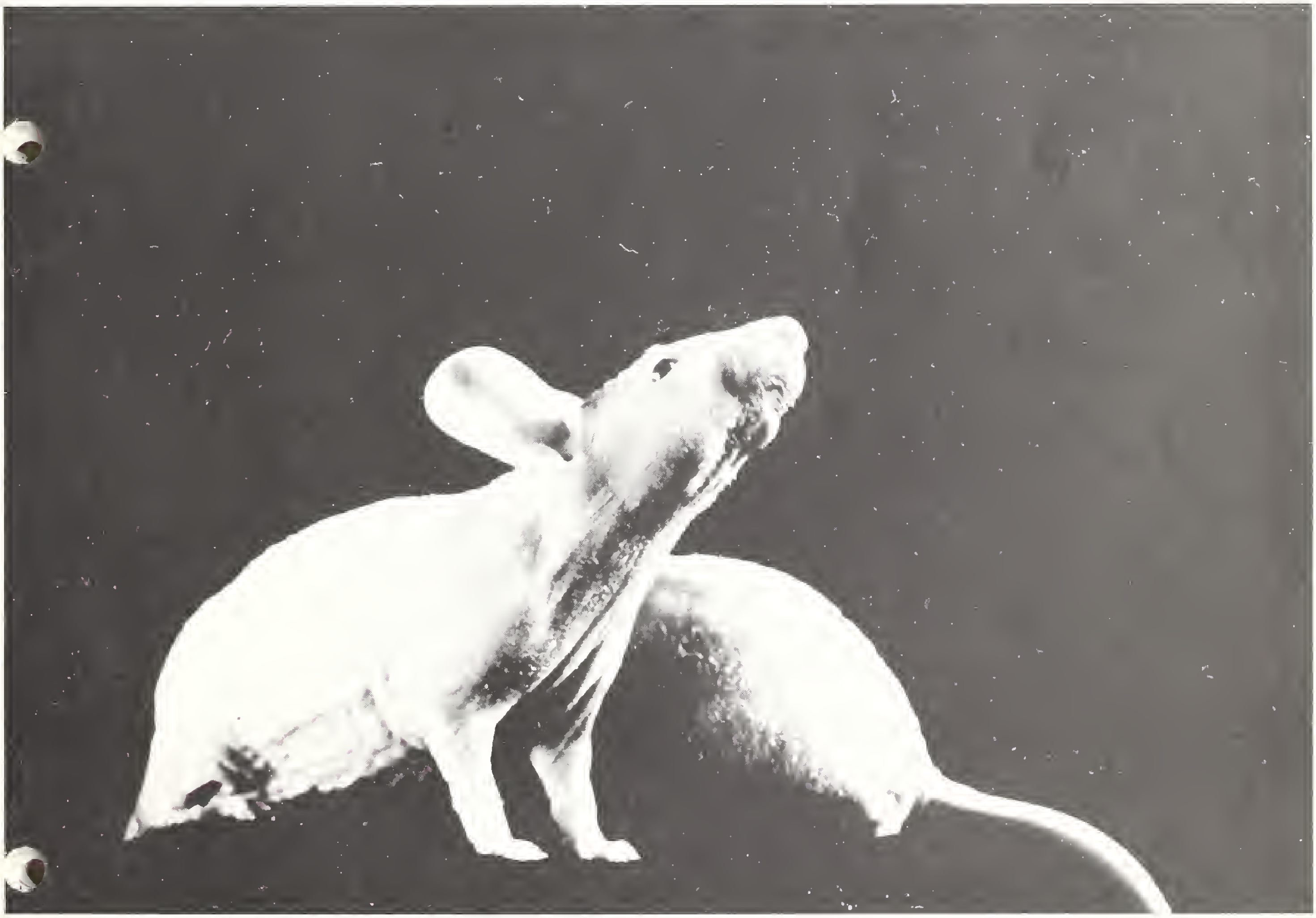

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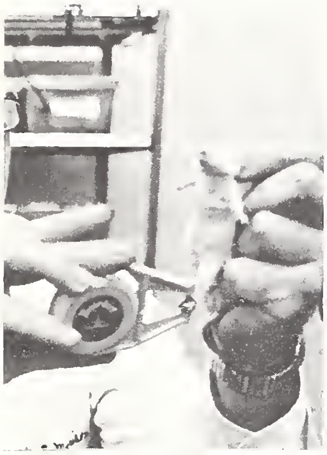
News&Features
from NIH

August 1981



Tropical diseases are the scourge of most of the world's population. They are as varied and complex as any group of diseases, requiring extensive investigation both in this country and abroad. At Johns Hopkins University in Baltimore, reseachers at the Tropical Medicine Center are employing a multidisciplinary approach to the problem in the hopes of developing new ways to prevent and control tropical illnesses.

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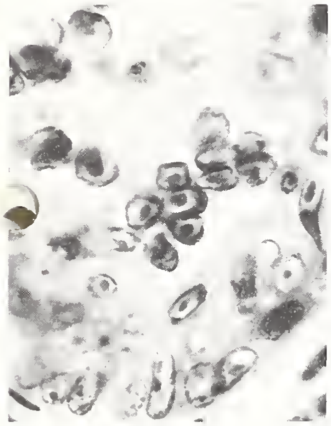

An epidemic of genital herpes appears to be sweeping the country. Some researchers believe that many adults are unaware they have the disease, thus unwittingly contributing to its spread. Research in prevention and treatment is beginning to offer some signs of hope for the victims of this sexually transmitted disease, the most devastated of which is the newborn.

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Television monitoring of patients with intractable epilepsy can provide physicians with the information they need to determine which drugs to select. By classifying a seizure type, a physician might prescribe a different drug or increase or decrease the dose of a drug that failed to control seizures in the past.

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DES, the substance found to cause vaginal cancer in some young women whose mothers were treated with the drug during pregnancy is providing scientists with clues about how some chemicals cause cancer. In animals, the drug seems to cause mismatched numbers of chromosomes, called aneuploidy, which may be a factor in the development of cancerous cells.

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Animals—a Major Scientific Resource—Should We Continue to Use Them in Research?

By Susan Gerhold

Animals have always played an important role in human health-related research and testing. In protecting human life, animals have contributed significantly in testing the safety and efficacy of new drugs and have been essential in helping researchers develop more sophisticated surgical procedures. They have also been instrumental in testing potential environmental toxins and thereby preventing significant disease and disability.

At a recent meeting held in Washington, D.C., scientists and administrators from various government agencies including NIH, university representatives, members of the animal welfare societies, and the general public, discussed the feasibility of using *in vitro* and/or mathematical models to reduce dependency on the use of animals in bioassays.

"The objective of the symposium was to present the current array of scientific perspectives on bioassay and distill them into a summary of the state of the art which should be useful to practicing scientists, to sponsors of research, to representatives of regulatory agencies, and to the general public," said Dr. William Raub, NIH's Associate Director for Extramural Research and Training, and moderator for the three day meeting.

He also stated that the symposium was designed to discuss improved testing methods and to sharpen the consciousness of health administrators and scientists in examining "the advantages, limitations, and prospects for improving commonly used research and testing methods."

Dr. Raub also outlined three principal themes to be discussed biological measurement using live animals; tests and systems using cell cultures and bacteria (*in vitro*); and mathematical and computation adjuncts to bioassay.

The bioassay issue involves weighing the risk to human health and safety against the cost of the testing as measured in time, money, and the lives of animals.

Congressman George E. Brown, Jr., (D-California) then ranking member, House Subcommittee on Science Research & Technology, opened the meeting expressing congressional interest in the possiblity of reducing the number of animals in research and testing. Several proposals are currently pending legislative approval, and one bill under consideration directs each agency which conducts or sponsors research and

NIH PHOTO #1684

NIH PHOTO #1685 Many of the animals used in research at the NIH are housed on a 513-acre facility located in the rolling countryside of Poolesville, Maryland.

NIH PHOTO #1686

testing involving the use of live animals to spend 30-50 percent of their animal research funds on developing and instructing scientists in non-animal methods.

Dr. Victor Morgenroth of the Food and Drug Administration reported on the recent activities of the Interagency Regulatory Liaison Group (IRLG). The group consists of representatives from the Consumer Product Safety Commission (CPSC), the Department of Agriculture (DOA), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Occupational Safety and Health Administration (OSHA). The IRLG standardizes and simplifies regulatory requirements for biological testing, thereby reducing the need to duplicate the same test within each agency. Recently published in the Federal Register (January 22, 1981, Volume 46, #14) are guidelines on the research and testing protocols for acute oral and dermal toxicity, acute eye irritation and teratogenicity. With these new guidelines, there will be no need to perform similar tests.

NIH PHOTO #1687

Although there are more than four million environmental chemicals existing today, only 6,000 have actually been tested in animals. According to Dr. Richard Griesemer, Director of the Biology Division of the Oak Ridge National Laboratories, animal testing is costly in terms of time, money, trained personnel, and resources. However, to better understand the effects on biological systems, animal testing must be done. Cell cultures are used in conjuncton with animal testing, he said, to observe the genetic, metabolic, and perhaps the carcinogenic effects that might occur. When using several test procedures (*in vitro*, *in vivo*) he said the researcher gets an overall view of the potential hazards these toxins might place on humans.

In vitro approaches were discussed in the second section of the symposium. One paper presented research on testing mutagens and carcinogens using short term *in vitro* assays. These assays provide estimates of damage, but do not fully evaluate the risk of a carcinogen on humans. A battery of tests would be more effective to compare and validate these risks, and at the same time produce fewer false-positive errors.

The development of monoclonal antibodies, a new procedure in which antibodies are produced from only one cell type, was Dr. Matthew Scharff's (Department of Cell Biology, Albert Einstein College of Medicine) topic. He stressed that "in addition to a major scientific advancement, hybridoma technology (which uses animal cells that produce specific antibodies) requires the use of far fewer animals for the production of specific antibodies." Dr. Scharff also stated that monoclonal antibodies are important in serological uses and tissue typing, in diagnosing infectious diseases, and in identifying specific tumor antigens and subsets of lymphocytes.

Opening the section on mathematical models, one researcher discussed research studies of the circulatory system focusing on the effects of blood pressure and cardiac output from renal deficiency and salt loading. Mathematical models, according to some researchers, give a more precise and efficient definition to experiments, but this test procedure can only be used as a powerful adjunct to animal experiments.

Another researcher discussed the serious consequences facing medical research if animal bioassays were not used. Often many major research projects depend on animal testing, as well as mathematical adjuncts to compare and support test results.

Dr. Raub summarized the meeting by saying that *in vitro* assays will be applied increasingly in several research and testing areas, but cannot be expected to replace whole animal studies in certain research projects such as toxicity studies in the foreseeable future. He also stated that while there are many reasons to strive to reduce the number of animals used in biological testing, until new methods are found and verified, animals will continue to play an important role in bioassay methodology.

He concluded the meeting with the suggestion that a special bioassay forum be created on a government-wide basis and indicated that, toward that end in part, a summary report of the proceedings of this symposium would be distributed to the various federal agencies whose programs involve the use of experimental animals. He also indicated that the NIH would follow-up on the suggestion of one of the speakers that the chimpanzee be awarded special protection from research risks because of the likeness to the human species. ■

Genital Herpes: The Venereal Disease in Hiding

By Maureen A. Miller
(student intern for the News Branch)

At the current estimated rate of one quarter to one half million new cases of genital herpes each year in the United States, one would think—and indeed some in the medical community suspect—that genital herpes is an epidemic disease. But some physicians question this notion because those who have monitored cases of genital herpes across the country have been unable to document any substantial increase in the disease since 1977. This perplexing problem is one of many that researchers face when they study genital herpes.

Physicians identified herpes, the common name for herpes simplex virus, as a venereal disease long ago. It was not until the 1970's, however, that they recognized the magnitude and severity of this sexually transmitted disease. Not all people are aware of the disease and those who are, and acquire it, do not always report it.

What is Herpes?

It is a very contagious virus that is usually spread by close bodily contact. The genital area and the mouth are the prime targets of infection. Once acquired in these areas, the virus can spread to other parts of the body, researchers caution.

There are two basic types of herpes infections: type 1 and type 2. Most cases of the genital herpes are caused by the type 2 virus, while most oral infections are caused by type 1. Researchers say, however, that both types of virus can infect any area of the body. This article will focus on genital herpes, the more serious of the two infections.

Two to 20 days after a person has been infected with the genital herpes virus (for the first time) sores appear at the site of infection. The sores may itch, burn or be quite painful. Symptoms may also include swollen glands, muscle aches and fever. Physicians refer to the first or "primary" attack of genital herpes as the active stage of the virus. Then, the virus leaves the sores and resides in certain nerve cells, forming a permanent reservoir of latent virus.

The Curse of Recurring Episodes

The latent period does not spell the end of a patient's misery. Researchers say the latent virus migrates periodically to the original site(s) of sores, where it reactivates the symptoms of active infection. Fortunately, recurring attacks are usually not as severe as the primary attack, but they can be very disabling. According to researchers, recurrences vary from patient to patient, not only in degree of severity but also in rate of return. Some patients only experience occasional attacks within a year, while others have recurrences as often as every few weeks.

People afflicted with genital herpes experience much psychological trauma as well as physical discomfort. In fact, physicians say that the psychological effects of genital herpes may be more crippling than the symptoms themselves. Patients' social behavior may change markedly and they may even experience severe depression. According to Dr. Dorland Davis, former director of the National Institute of Allergy and Infectious Diseases (NIAID), genital herpes is a more serious problem than it is given credit for. "It's not a killer disease," Dorland said, "but it does make people miserable."

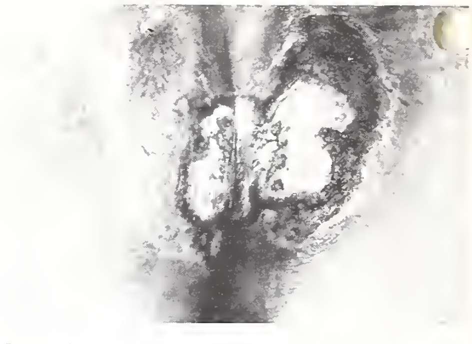
Epidemiology and Transmission

Perhaps ten percent of the population of the United States—more than 20 million persons—has been infected with genital herpes at some time during their lives, estimates Dr. Stephen E. Straus of the NIAID. Moreover, researchers now recognize that some individuals infected with the virus do not develop recognizable symptoms. What this means is that epidemiologists cannot monitor the total incidence of genital herpes in this country even if all affected individuals report symptoms. The highly contagious herpes virus can be spread by asymptomatic carriers as well.

The implications of this situation are serious. According to Dr. Mary E. Guinan of the Centers for Disease Control in Atlanta, Georgia, epidemiologic data suggest that there is a high percentage of persons with genital herpes who do not know they have the disease and are unwittingly contributing to its spread.

An infected individual can spread the virus when sores are present and they have intimate contact with another person. The contagious period of the virus is called the period of "viral shedding," that is, when a person secretes virus from their sores. Researchers do not know, however, if, and for how long, a person can spread infection after the herpes sores have disappeared.

Guinan speculates the "patients with genital herpes are more likely to be middle-income people who do not go to VD clinics." She added, "the epidemic may be occurring in private offices" where there is no mandatory reporting or surveillance. In essence, the social stigma of genital herpes makes it hard to track carriers of the disease.



Genital herpes in an immunocompromosed individual. Lesions on the buttocks are typical of this disease. NIH PHOTO #1688

The Problem of Recurrence vs. Reinfection

What spurs recurrences of genital herpes infection remains a mystery. Straus said "researchers have no good answers yet" about the mechanism behind recurrences of the virus. At present, then, physicians cannot prevent recurrences. They can only cite several situations or conditions that may precipitate a recurrence such as sexual contact, emotional upsets or stress, and infections other than herpes.

The problem of recurrences vs. reinfections poses yet another puzzle for researchers. A person infected with eith[illegible] type of herpes develops an immunity [illegible] the type of herpes acquired in the primary infection. This immunity is specific to the type of herpes acquired, however; it does not apply to a primary attack by the alternate type of virus, according to researchers. Thus, what may appear to be a recurrence of type 1 herpes may in reality be a reinfection by type 2 herpes, or vice versa.

Reinfections can complicate a doctor's diagnosis of the course of a patient's disease. Straus observed that "clinically there is little difference between recurrences and reinfections" regarding symptoms. He added that reinfections with herpes are more likely to occur when infected individuals have multiple sex partners.

Experimental Treatment: Antiviral Drugs

Although there is no current cure for genital herpes, researchers are investigating various experimental drugs to treat symptoms. They stress that early treatment is crucial to obtaining any possible benefits from these drugs.

At a recent workshop on genital herpes at NIH, participants cited immediate goals for treating the disease: to reduce the severity of both primary attacks and rec[illegible]rences; to decrease the frequency [illegible] recurrences; and to reduce the spread of the disease.

Antiviral drugs appear to be the most promising treatment thus far. Researchers have tested several of these for safety and efficacy in animals, of which the major ones are: adenine arabinoside (ara-A); adenine arabinoside monophosphate (ara-AMP, a derivative of ara-A); 2-fluoro-5-iodoaracytosine; and acyclovir. Investigators have treated humans with ara-A, but it has not proven effective for genital herpes in the adult. However, it does appear to very effective for treating herpes simplex infections in the newborn.

Acyclovir is one of the most promising antiviral drugs for genital herpes because it appears to be effective with few side effects. Straus is one of the investigators conducting clinical trials of acyclovir. For the past few years, he has been treating several patients who suffer from serious recurrences. He maintains that among current antiviral drug options it appears to be the most ideal because it is both "potent" and "selective," that is, acyclovir attacks virus-infected cells, but is relatively nontoxic to normal cells. Straus is currently testing an oral form of acyclovir for convenient administration. At present, doctors must administer an antiviral drug intravenously or inject it into the muscle for the drug to reach the infected cells.

Despite the promise of acyclovir, Straus cautions that it can only "suppress" the genital herpes virus at this time; it cannot prevent recurrences. He is trying to increase the ability of the drug to suppress recurrences, though, by giving patients "lower doses of acyclovir for longer periods of time."

Interferon is another form of treatment which may be promising and which researchers are currently testing. It is a naturally-occurring substance in man and animals that fights cell infection. According to Dr. George J. Galasso of the NIAID, data from previous human trials of interferon for oral herpes indicate that it reduced the severity as well as the rate of recurrences by about 50 percent. These findings spurred researchers to see if interferon would have a similar effect on patients with genital herpes.

Dr. Monto Ho, an NIAID contractor from the University of Pittsburgh, recently started the first clinical trial of interferon for genital herpes. Galasso said this study will test two variables: "the role of interferon in modulating (decreasing the severity) primary genital herpes" and in reducing the severity and rate of recurrences. Ho plans to treat 40 women who have genital herpes and are not pregnant. The study should take one to two years to complete, said Galasso. It will be sometime before researchers can draw any conclusions about the safety and efficacy of interferon for genital herpes, he added.

The Possibility of a Vaccine

Perhaps the most promising, though most distant, of proposed treatments for genital herpes is a vaccine. The goal of such a vaccine would be, at the very least, to eliminate recurrences and, at best, to prevent the disease altogether.

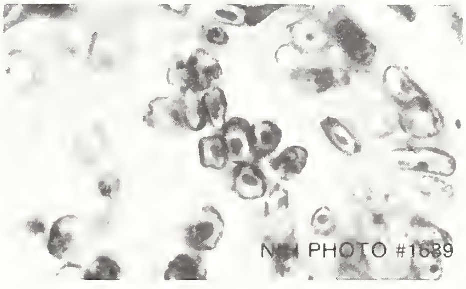
A team of researchers at Merck, Sharpe, and Dohme, Inc. (MSD), is under contract to the National Cancer Institute to develop a vaccine composed of glycoproteins (a class of proteins that includes a carbohydrate group) obtained from the genital herpes virus. Dr. William P. Allen of the NIAID explained that MSD's vaccine is a "subunit vaccine" that is not infectious and does not contain any DNA material of the virus that may possibly promote cancer. Viruses can cause different types of cancer in animals. Although researchers have not found any cancer viruses in humans, they have detected an association between genital herpes and cervical cancer. They report that women with genital herpes are four times more likely to develop cervical cancer than women who do not have this disease.

Researchers at MSD do not know exactly how the vaccine works, but they propose that massive amounts of antibodies present in the vaccine may prevent recurrences. In effect, they contend that recurrences may be due to an insufficient amount of antibodies rather than a defective immune response. This is only one theory, nevertheless, and researchers stress that the role of the immune system in fighting recurrences is not clear.

In addition to injecting animals with the vaccine, MSD has tested several individuals for their initial reactions. Preliminary data indicate that the vaccine has a substantial effect on decreasing the severity and the rate of recurrence, according to researchers at the drug company. Allen added, however, that controlled clinical trials must be conducted to obtain both reliable and long-term data about the vaccine's safety and efficacy.

Merck, Sharpe, and Dohme, Inc. plans to conduct the first clinical trial of the vaccine very shortly. Forty individuals with genital herpes will be selected to participate.

If the experimental vaccine proves safe and effective, can it be expected ultimately to prevent the infection itself? Allen observed this is probably not an "achievable goal" because of the nature of the herpes simplex virus. To illustrate the nature of the virus, he offered the example of infant herpes. As is often the case, a woman may not be aware she has genital herpes while pregnant. She will transfer her antibodies to the virus to her baby via the placenta. Allen explained, however, that this is not an absolute safeguard for the infant. When the virus comes in contact with the baby at birth, it may infect the baby by a route that escapes contact with the antibodies. If this happens, the infant becomes infected and may develop serious disease.



Normal cells in culture are ballooned in size due to infection by the herpes virus.

The vaccine also raises the question of who should receive it. Since it is a prophylactic (form of preventive medicine), researchers must first determine which populations run the risk of acquiring genital herpes. Until researchers can get a handle on accurate epidemiologic data, this will not be possible.

A final consideration about the vaccine is how it will fare against antiviral drugs. Namely, will it be a viable alternative to chemotherapy if eventually marketed? Allen said the vaccine will not necessarily be more effective than antiviral drugs, or effective across the board for all individuals with genital herpes. Mode of therapy, as well as severity of disease, may be specific to the individual, he explained.

The Need for Public and Professional Awareness

The need for research to develop better methods of controlling primary infections and recurrences, and ultimately preventing recurrences, has been addressed. Research is not, however, the entire answer to checking the suspected epidemic of genital herpes in this country. The 1980 Status Report on Sexually Transmitted Diseases, published by the NIAID, adds that doctors and medical students must be better trained to diagnose and treat herpes simplex infections.

Dr. King K. Holmes, a leader in genital herpes research, and his associates conducted a survey of American medical school curricula and found that only 15 percent offered any clinical training in sexually transmitted diseases. Holmes also noted that public health department clinics for sexually transmitted diseases in the United States are not presently equipped to diagnose the array of venereal diseases that exists throughout the country. Almost none of the clinics have any diagnostic tests for herpes simplex virus, he said.

Finally, the public must be made aware of the existence and consequences of genital herpes. A substantial segment of the population has never heard of this venereal disease, although it is allegedly increasing faster than either gonorrhea or syphilis, according to the 1980 Status Report. If increased medical training and research on genital herpes go hand-in-hand with increased public awareness of this disease, we may be on our way to controlling this devastating venereal disease. ■

Herpes in the Newborn

By Maureen A. Miller
(student intern for the News Branch)

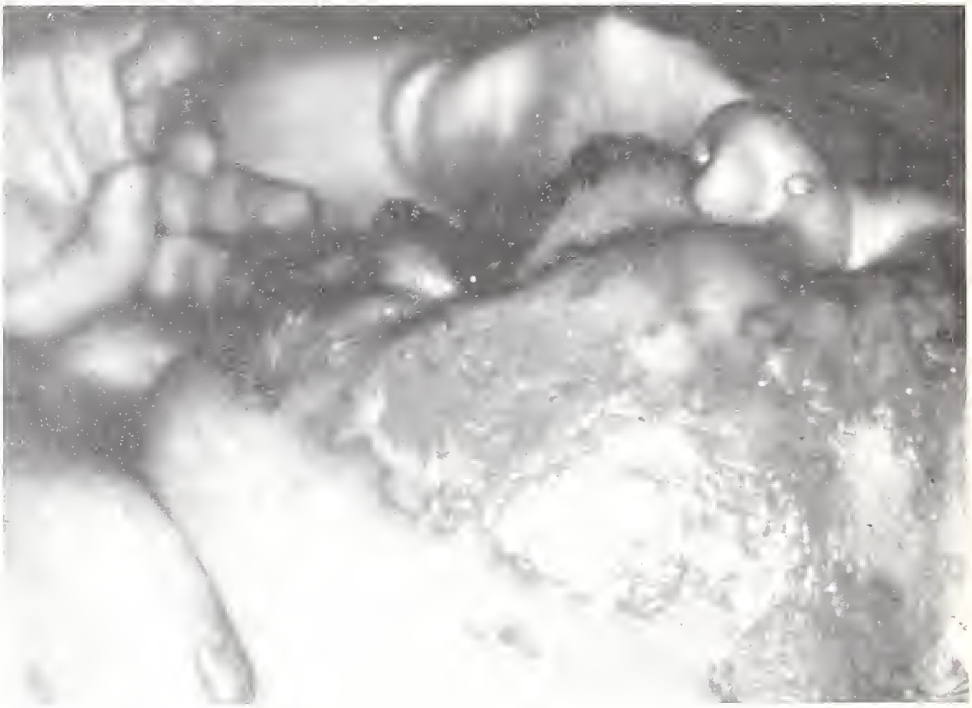
The rapid increase of genital herpes in this country has taken its toll on the newborn too. According to researchers, one to five infants out of every 10,000 live births are born with genital herpes infection each year in the United States.

Pregnant women who have genital herpes may transmit the infection to their babies via the birth canal at the time of birth. The problem is that about 70 percent of pregnant women with genital herpes have no apparent symptoms of infection within eight weeks of delivery.

Although doctors don't know the exact probabilities of a baby contracting genital herpes from its mother at delivery, they report that the chances may be as high as 50 percent if infected mothers are shedding virus during this time. Moreover, data suggest that pregnant women with genital herpes are two to three times more likely to miscarry or deliver earlier than pregnant women who do not have herpes.

Herpes infection in the newborn is markedly more serious than in the adult. Even a low level of virus can readily infect the newborn, and as in the adult, symptoms may not be immediately obvious. If infected newborns are not treated promptly, death or serious and long-term disorders usually result, said Dr. Charles A. Alford Jr., a participant at the recent NIH workshop on genital herpes.

Alford specified three categories of herpes infection in the newborn: localized, multiple organ and brain infections. Localized infection refers to the eye, the mouth, the skin, or combinations of them. Multiple organ infection affects one or more organs and possibly the central nervous system. The death rate is very high, said Alford, and those newborns who do survive rarely recover without damage to the central nervous system if it is affected. Brain infection, also known as herpes encephalitis, is confined to the brain, and as in organ infection, the death rate is extremely high. If a newborn with this infection does survive, brain damage such as mental retardation is almost inevitable. Alford commented, "Prolonged or severe morbidity is a major problem in these infants."


This newborn suffers from neonatal herpes type 2. Herpes sores are present around the mouth, eye and other areas of the skin, indicating a localized infection.

NIH PHOTO #1690

"Ara-A is the only drug that has been shown to have any effect on the newborn with herpes," said Dr. Richard J. Whitley, a researcher supported by NIH at the University of Alabama. He added that ara-A therapy for the newborn has been very effective, particularly for organ infection and herpes encephalitis where it has increased the newborn's chances of survival three times. Whitley added that when clinical trials of acyclovir; ara-AMP; 2-fluoro-5-iodoaracytosine; and interferon are completed, doctors may have further clues about the safety and efficacy of these potentially promising drugs for the newborn as well.

When a physician does detect genital herpes in a pregnant woman, he performs a culture to determine if the patient is shedding virus. If the culture is positive he may opt to deliver the baby by Caesarean section to prevent exposure to the virus in the birth canal. At present, this is the only way infant herpes can be prevented if diagnosed prior to delivery. Whitley observed, "There are no approved experimental antiviral drugs that can be given to the mother to prevent viral shedding before delivery."

Researchers cite the need to investigate alternatives to the Caesarean section, but the more pressing need right now is to detect genital herpes in all pregnant women who are infected. The latter goal can be achieved in two ways: patient cooperation and improved diagnostic techniques to detect asymptomatic carriers of the virus. Doctors stress that if a woman is pregnant and knows or suspects she has genital herpes, she should notify her doctor immediately to plan the safe delivery of her child. ■

Neurological Disorders in the Elderly: Stalking the Statistics

By Ray Fleming

Since ancient times, the relationship between disease and advancing age has been so strong that many disorders were simply considered a natural part of the aging process. But thanks to modern research, especially in the neurosciences, we now understand that a number of the problems that appear as the body grows old are due to specific treatable diseases and not solely to the aging process.

Much of what we know about the extent of neurological disease in the elderly comes from studying large populations of people. These studies are carried out by neuroepidemiologists, who look at patterns of brain and nervous system disease in populations.

Dr. Bruce Schoenberg, chief of the National Institute of Neurological and Communicative Disorders and Stroke's neuroepidemiology section, reports in a paper recenty published in *Seminars in Neurology* that people age 65 or older are at a particularly high risk for nervous system disorders, and gives data to support this statement. He indicates the magnitude of the problem and reviews the statistics for four common nervous system disturbances among the aged: the dementias, stroke, Parkinson's disease and brain tumors.

Deaths from the dementias from 1968 through 1973 numbered 3,378 in the United States, according to one study. This is probably a low estimate, says Dr. Schoenberg, since deaths involving the dementias may be attributed in the mortality statistics to some other underlying cause.

The most current data on the rate of occurrence of the dementias comes from a study of the residents of Rochester, Minnesota from 1960 through 1964. Of 18,556 people over 29 years old, 102 developed the disorder during the five-year period, yielding an average annual incidence of 110 new cases per 100,000 individuals. Again, Dr. Schoenberg cautions that these figures only include reported cases of the dementias; therefore, they probably underestimate the magnitude of the problem.

The Schoenberg report relates several other observations on the dementias. The rates of occurrence for all dementias, including Alzheimer's disease, increase with the age of the group being studied. In addition, the incidence for cases of dementia diagnosed as Alzheimer's disease is greater for women than for men. The reasons for this difference are being investigated.

Stroke is the third leading cause of death in the U.S. and a major cause of illness, says Schoenberg in his report. Most stroke death rates from developed countries in North America and Europe are close to 100 deaths per 100,000 persons in a given year. For every five-year increase in age, notes the report, the stroke death rate doubles. Slightly more men than women die from the disease, and more black Americans than white; the U.S. death rate from stroke is highest in the southeastern portion of the country.

On the positive side, however, Dr. Schoenberg relates some encouraging news: both the death rates and incidence of stroke are declining in the U.S. and in other developed countries. Better control of stroke risk factors such as hypertension may be the reason for the decline.

NINCDS neuroepidemiologist Dr. Bruce Schoenberg studies patterns of nervous system disorders in the elderly.

NIH PHOTO #1691

Parkinson's disease is another common neurological disorder receiving considerable attention from neuroepidemiologists. Despite the fact that Parkinson's disease, like dementia, is frequently omitted by mortality statistics in an underlying cause of death, several important patterns have been discovered. The death rate is negligible for people under 45. The rate increases steadily with age, reaching a peak at age 75-84; and then declines among the oldest age groups. Dr. Schoenberg also observes that mortality rates for whites are 3-4 times that for nonwhites.

Interestingly enough, the incidence of Parkinson's follows the same pattern as the death rate: after age 30-40, it increases with advancing age to a peak at about age 75, with a decline in new cases after that. Dr. Schoenberg and others speculate that such a pattern, which is different from that of dementia and stroke (where incidence does not peak and then fall), could be an important clue to the cause of Parkinson's disease. Perhaps the number of susceptible individuals begins to decrease at the age where the peak occurs. The pattern could also mean that susceptible individuals are exposed to a possible disease-causing agent for a certain number of years. Another possibility is that many cases of Parkinson's disease in those over 75 are not being correctly diagnosed.

The occurrence of primary brain tumors, which is surprisingly frequent among older individuals, has also been investigated by neuroepidemiologists. Dr. Schoenberg reports that males have a slightly higher annual death rate for nervous system tumors than females, based on the results of an international comparison. Data on both deaths and new cases of brain tumor show similar patterns: a small peak in childhood, followed by a higher, sharper peak in adult life, and then a decline in the oldest age groups.

In the next 20 years, the number of people in the U.S. aged 65 and over is expected to increase from 25 to 32 million. That is a significant addition to an elderly population that neuroscientists are trying to keep healthy and productive. The statistics on these four and other neurological disorders affecting the elderly provide valuable information for scientific researchers, health care professionals, and the general public. Such data can provide clues to investigators about the causes of disease, and can promote better understanding and more accurate reporting of nervous system disorders in the elderly by physicians and families of patients. ■

Tropical Disease Research Expands at Johns Hopkins

By Dr Margie F Taylor

An intensified effort to find better methods to combat tropical diseases in developing countries has moved into full operation through the establishment of the Tropical Medicine Center at the Johns Hopkins School of Hygiene and Public Health in Baltimore.

"The problem with tropical diseases is that the countries in which they occur are generally poor and have little advanced scientific research," says Dr. Howard Goodman, the Center's director and the founding director of a World Health Organizaton (WHO) tropical diseases research and training program. "Malaria and some other tropical diseases continue to spread, and Americans who travel to these countries come home with a variety of ailments. It is an essential area of public health at home and in tropical countries."

Tropical diseases plague one billion people each year. An estimated 400 million humans have malaria or suffer from schistosomiasis, while 300 million have filariasis. That group of parasitic diseases includes onchocerciasis—which affects 40 million people. In Latin America, 12 million people suffer from Chagas' disease. Its African counterpart, sleeping sickness, kills three million cattle each year. Victims of leishmaniasis (another parasitic disease) number in the tens of millions. Approximately 12 million people have leprosy.

The Center at Johns Hopkins, which received its start-up support from NIH's Division of Research Resources through its Biomedical Research Support Grant program, contains insects, parasites, and fungi originating from exotic tropical lands. But the glamor of the tropics is forgotten as scientists delve intensely into the intricacies of tropical disease transmission.

In one windowless room, 30 different kinds of mosquitoes, native to the tropic islands of Polynesia, are buzzing around in confined spaces. Fish tanks in another room are populated with snails from Brazil and other equatorial countries. A freezer in the basement is filled with parasites that began their life cycles in fast-flowing mountain streams in Guatemala.

Major investigations, still in progress, are beginning to produce results. A biomedical-pharmacologist working with NIH and with support from the Agency for International Development has developed what may be a simple and inexpensive treatment for schistosomiasis (snail fever), one of the world's major tropical parasitic diseases. The first human trials are just beginning at Hopkins, although the Chinese government has used the drug with good results on more than 100,000 people. The drug is effective with a single oral dose and costs about $1 a dose.

Dr. Thomas Trischmann, assistant professor of pathobiology at Johns Hopkins, handles cultures of *Trypanosoma cruzi* under a safety hood. This organism causes Chagas disease, which affects some 12 million people in Latin and South America   NIH PHOTO #1692

Another researcher has developed a method of diagnosing "river blindness," a tropical disease that has caused blindness in two million people worldwide. The method uses a new skin test to diagnose [illegible] diseases, which is caused by parasite worms carried by biting flies.

The Center has helped initiate a major joint endeavor with WHO and the Wilmer Institute of Baltimore to examine the leading worldwide causes of sight-destroying diseases.

Dr. Goodman recently completed a WHO consulting assignment in Thailand designed to help coordinate national health research planning. Among the areas addressed were malaria, diarrheal diseases, and laboratory support to develop simplified methods so that trained non-professional village health volunteers could learn to test for tropical diseases.

"A trained village volunteer can take a finger-prick blood sample on a piece of filter paper, dry it, and send it to a central lab where tests could show whether the patient has been exposed to a specific tropical disease," he explains. "The U.S. Centers for Disease Control now gets these dried samples from all over the world to check for malaria. This type of testing can be done for epidemiologic surveillance of other diseases as well."

A Hopkins-trained physician and immunologist, Dr. Goodman became director of the Tropical Medical Center in [illegible] 1977 after serving as research director [illegible] WHO in Geneva. Since returning to Johns Hopkins, he has helped form multidisciplinary scientific research groups in the Johns Hopkins medical institutions. Laboratory and clinical scientists skilled in parasitology and other infectious diseases, drug trials, immunology, biochemistry, molecular biology, and genetics work together with their colleagues in tropical countries to seek out cause, cures and methods for preventing tropical illnesses. ■

Involved in leprosy research, Dr. Norman Morrison of the Tropical Medicine Center measures delayed type hypersensitivity in mouse foot pads, where the organism that causes leprosy, *M. leprae*, has been growing. Studies of the immunologic aspects of leprosy offer unusual promise for understanding not only leprosy but other diseases, such as tuberculosis. NIH PHOTO #1693

Dr. Milan Trypis, professor of pathobiology at Johns Hopkins, stands near mosquito cages where insect colonies are reared for tropical disease research, in particular, malaria. The cage portals are made to allow researchers to put their hands in without risking loss of the insects. NIH PHOTO #1694

All Photos
by William Denison

Intensive Epilepsy Monitoring: Help for Patients with Intractable Seizures

By Diane Striar

After 14 years of uncontrolled epilepsy, Marcy Key's* seizures are disappearing.

"That's the best news I've had," says the young woman, who used to have daily seizures. Since Marcy's discharge last September from a study of intensive epilepsy monitoring at the NIH Clinical Center, she has had only two or three seizures a month.

Marcy is one of approximately 100 patients who have participated in a research project of intractable epilepsy conducted by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). The study has been in operation since 1975.

The therapeutic technique that has helped control Marcy's and other patients' epilepsy is a detailed video information system which simultaneously films seizures and records their electrical activity as measured by an electroencephalogram (EEG). The system also includes frequent blood tests to determine how the patient metabolizes the drugs used in treatment.

Seizures are filmed by two television cameras—one providing a full shot of the patient, the other a close-up view. Both images are displayed simultaneously on a video screen along with the patient's EEG recording. The EEG is obtained from a radio telemetry transmitter contained in a plastic headband worn by the patient. The transmitter carries the brain wave signal to the television screen from eight electrodes placed on the patient's scalp.

The four epilepsy patients currently in the study are monitored twice a week for 6 hours at a time. By studying the resulting videotapes, NINCDS neurologists are able to differentiate the types of seizures that these patients have.

Identifying the seizure type is the most important step in determining which anticonvulsant drug to prescribe, according to Dr. Roger J. Porter, chief of the Epilepsy Branch of NINCDS's Neurological Disorders Program. Dr. Porter views intensive monitoring as a "tool, an extension of the doctor's ability to diagnose and to apply appropriate therapy."

Seizure classification, combined with a neurological examination, thorough study of the patient's history and an analysis of the level of anti-epileptic drugs in the patient's blood, allows NINCDS physicians to revise the treatment plan as needed. The physician might prescribe a different drug, for example, or might increase or decrease the dosage of a drug that failed to control seizures in the past.

Intractable Epilepsy Patients Only

Most people with epilepsy do not require the battery of tests and film sessions involved in intensive monitoring. About 50 percent of all epileptic seizures are controlled with medication and 3 percent are partially controlled. Marcy's case, however, is typical of the over 200,000 epileptic patients who have not been helped by conventional drug therapy. For many of these "intractable patients," seizure types were incorrectly classified and ineffective medication or dosages prescribed.

Marcy, for example, was on various combinations of carbamazepine, phenobarbital, mesantoin, and chlorpromazine before coming to NIH. After 2 months of intensive monitoring, she was placed on a more effective dosage of carbamazepine. The result: greater control and fewer side effects. "I'm not as drowsy now," she says. "My concentration has improved, so I can do more reading."

Unlike Marcy, who had three different types of epileptic seizures, some patients diagnosed as having intractable epilepsy actually do not have the disorder. The seizures of these individuals are not associated with any unusual electrical activity in the brain, a primary requirement for an epilepsy diagnosis. Intensive monitoring confirms that the EEGs of these patients are normal during seizure activity, and that their seizures are psychogenic or hysterical—not epileptic—in nature.

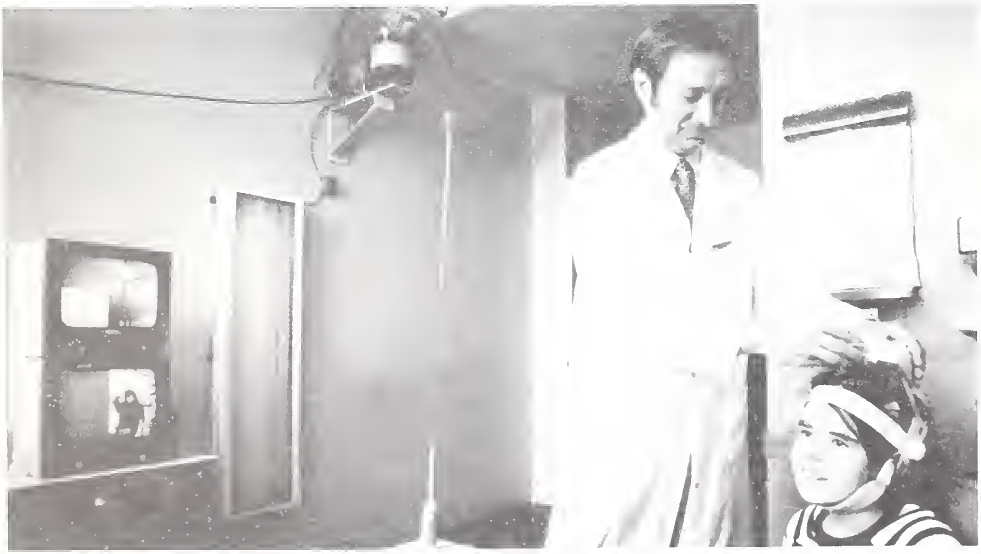
Getting a Handle on Seizure Types

The need to film seizures is tied to the nature of epilepsy and the difficulties encountered in studying this disorder. "One of the problems that has always plagued the study of epilepsy is that symptoms are episodic," says Dr. Porter. "You can look at the patient three times a day and see nothing. With continuous videotape recording, we can get a handle on seizure activity."

Research is also made difficult by the heterogenous nature of epilepsy. The International Classification of Epileptic Seizures lists eight types of generalized seizures—including the tonic clonic or grand mal—and 10 types of partial seizures such as the psychomotor.

A Treatment Revolution

According to Dr. Porter, intensive monitoring is revolutionizing the treatment of severe epilepsy in this country. An increasing number of doctors are referring their "intractable" cases to some 30 intensive monitoring units around the country. Six of these projects are located



Dr. Roger Porter, chief, Epilepsy Branch, NINCDS, adjusts telemetering equipment worn by a child with epilepsy. Equipment broadcasts EEG, which is picked up by an antenna (center) and fed into equipment that correlates tracings with the patient's movements as recorded via a television camera (above). Telemetering permits the patient to move freely and normally while scientists study action of various experimental drugs. NIH PHOTO #1695 at NINCDS-supported Comprehensive Epilepsy Research Programs.

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*Names of patients in this article have been changed.

Evidence of the new technique's effectiveness can be found in a recent two-year follow-up study of 74 of the 100 Clinical Center patients who were monitored between 1976 and 1980. The average amount of time spent in the hospital was 12½ weeks. When discharged, 67 percent of the patients had fewer seizures, 73 percent had decreased drug side effects, and 30 percent had improved their personal or work situations. Some patients found jobs; other were able to live more independently or got along better with their relatives. The benefits of intensive monitoring were still being felt two years later. Follow-up evaluations showed that a majority of the patients still had fewer seizures and reduced drug side effects. An even greater number of patients (41 percent) had improved their job status or their relationships with friends and family.

Even if a patient doesn't have seizures while being monitored at the Clinical Center, staff neurologists can help by measuring blood levels of medication and altering the dosage or the drug—or both.

One patient who falls into this category is 24-year-old Anna Bezilli from Long Island. Although she has been at NIH since last January, she has had very few seizures while hospitalized at 5-West Clinical Center-even when taking previously ineffective drugs. Her seizures increase, however, when she goes home to visit, a phenomenon she attributes to stress.

The Clinical Center Family

While the doctors continue to alter Anna's medication in the hope of arriving at the combination that will continue to control her seizures when she goes home, the thin, brown-haired woman is enjoying "a nice little break away from home."

Anna's days at the Clinical Center are spent working on arts and crafts and answering the phone in patient activities. On the two days a week she is monitored, Anna sits in front of the cameras, reading and watching television.

All of the epilepsy patients are visited by a social worker and some participate in occupational or physical therapy. Like former patient Marcy, Anna views the time spent at NIH as a chance to learn about epilepsy. "When I came to NIH, it was the first time I ever saw someone have a seizure," she says.

Anna, like Marcy and another former patient Sharon Drake, describes the patients and staff on 5-West Clinical Center as a "little family."

"There's definitely a family atmosphere," concurs Dr. Porter, who recalls that two patients met on the ward, fell in love, and married.

Former inpatient Sharon, who was Marcy's roommate on 5-West, says: "If I had a problem—any problem—I could call on a nurse just to talk."

Sharon could also count on Marcy, who came to NIH equipped with a medical dictionary, to explain medical jargon. "I translated what the doctors told her," says Marcy who considers the friendship that began at the Clinical Center very special. "It was the first time I'd ever been close friends with someone who had epilepsy," she adds, "I helped Sharon out at NIH and she helped me."

The two women continued their mutual support when Marcy moved into the Rockville, Maryland house owned by Sharon and her husband. Marcy, who rarely has seizures, now helps Sharon—making sure she doesn't injure herself during a seizure. Sharon still has frequent seizures—about 500 last year—but she is experiencing fewer drug side effects. Information obtained during intensive monitoring, in conjunction with the results of a PET (positron emission tomography) scan, indicates that Sharon is a likely candidate for surgery.

"Right now, I feel as if I'm in a holding pattern," says Sharon, who is waiting to take some final diagnostic test which will confirm whether surgery is a practical step. "I trust that the doctors know what's best...I'm placing my head in their hands."

While Sharon awaits their decision, housemate Marcy, who is now practically seizure-free, is exploring job and school opportunities. She wants to attend night school to "build up my math and reading."

Although Anna, who is still on the ward, would like to go home soon, she values her NIH experience. "I have more hope now," she says, "and that's what makes you a person."

There is currently a 6-month waiting list for the intensive monitoring study. Patient eligibility requirements include a *history of complex-partial epilepsy* and *frequent seizures. Contact the Patient Referral Service at (301) 496-4891 for admission information.* ■

DES Research May Shed Light on How Some Chemicals Cause Cancer

By Hugh James Lee

Scientists studying diethylstilbestrol (DES) have found that its mechanism of causing cancer in a model system using animal tissue cultures gives new insight into how some chemicals may cause cancer. Like other chemical carcinogens, DES causes the cancerous transformation of these isolated cells; however, unlike most other established chemical carcinogens, DES does not display mutagenic activity when tested on two gene markers used to detect mutagenic action. Instead, studies at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina determined that DES in this model system produced a mismatching of chromosomes called aneuploidy which in turn may be a key factor in the development of these cancer cells.

DES was used in the 1960's as a therapeutic drug for expectant mothers and until 1979 as a growth enhancer in beef cattle. Now greatly restricted in use as a drug and banned as an agricultural feed additive by FDA, DES had become a tool and a focus for research in reproductive and developmental toxicology, including birth defects research, immunology studies, and in research on the mechanisms of carcinogenicity.

Earlier research has shown DES to cause vaginal cancer in the daughters and genital dysfunction and malformation in male offsprings of women who took it during pregnancy. The recent study on DES's role in causing cancer was published in the June 19, 1981 issue of *Science*, in a paper titled "Diethylstilbestrol Induces Neoplastic Transformation in Cultured Cells Without Measurable Somatic Mutation at Two Loci," by J. Carl Barrett, Ph.D., of the Environmental Carcinogenesis Group of the Laboratory of Pulmonary Function and Toxicology, Ms. Annette Wong and John A. McLachlan, Ph.D. of the Transplacental Toxicology Group in the Laboratory of Reproductive and Developmental Toxicology all at NIEHS.

The ability of a substance to change the genetic material of cells, known as mutagenicity, is strongly associated with the development of cancer. The association is so strong that mutagenicity tests, notably the Ames test using bacteria, are widely supported as tools to screen suspect substances. If in the tests, the agents display mutagenic activity, they become candidates for carcinogenicity testing. The NIEHS research team wondered if the failure of DES to show mutagenicity in bacterial cultures might be due to factors which are present in cells of higher animals. Using hamster cells in culture they demonstrated that again DES showed no measurable mutagenicity in these cells.

The paper's abstract notes, "While diethylstilbestrol was as active as benzo(a)pyrene (a known mutagen and carcinogen) in inducing (cellular) transformation, it failed to induce mutations at two conventionally studied loci (gene sites on the chromosome). These results suggest that diethylstilbestrol may transform cells in the absence of gene mutations."

Instead of gene mutation, DES was found to cause mismatched numbers of chromosomes, an effect called aneuploidy. Normally, chromosomes occur only in perfectly matched pairs. This observation made in tissue cultures mirrored clinical findings made elsewhere of aneuploidy in the female offspring of DES-exposed women; this aneuploidy was observed in the precancerous dysplasia in their reproductive tracts. Since other carcinogens can induce aneuploidy, these studies with DES should stimulate new thinking about how some chemicals cause cancer. ■

Male Contraceptive Mechanism Pinpointed in Gossypol

By Hugh James Lee

Researchers at the National Institute of Environmental Health Sciences (NIEHS) have begun to unfold the biochemical mechanism of a promising male contraceptive drug, gossypol. Dr. Chi-Yu Lee of the Laboratory of Environmental Chemistry, and Dr. Heinrich V. Malling, Chief of the Laboratory of Biochemical Genetics, have discovered that gossypol is a preferential inhibitor of an important enzyme, lactate dehydrogenase-X, crucial in function of sperm in the testis. This interesting discovery now enables investigators to work toward redesigning or restructuring this drug to enhance its anti-fertility potential and decrease or eliminate any undesirable side effects.

Gossypol first became identified as an anti-fertility agent as the result of Chinese investigations in the 1950's. Scientists, puzzled by the extremely low birth rates in a particular geographic area, finally related the phenomenon to the peoples' exclusive use of crude cotton seed oil for cooking. Exploring further they determined that the active agent in the oil was gossypol, a naturally occurring yellowish phenolic compound found in the seed, stem, and root of the cotton plant.

One exciting aspect of the NIEHS discovery in terms of developing a male contraceptive drug is that gossypol has an effect only on certain sperm-generating cells and sperm itself, but has little effect on sex hormone levels or libido in males.

During the development of mutation monitoring and biochemical genetic programs at NIEHS, scientists became interested in gossypol's effect on sperm and sperm-generating cells. They looked at gossypol's effect on the testis-specific enzyme, lactate dehydrogenase-X, since it plays a critical role in both aerobic (with oxygen) and anerobic (without oxygen) metabolism of sperm and sperm-generating cells.

Dr. Malling explained, "By simple biochemical assays, we have shown that the activity of the enzyme is inhibited by a relatively low concentration of gossypol. We have observed this selective inhibition for this enzyme in tissue from a variety of species including rodents and humans."

But gossypol also has its drawbacks. NIEHS scientists found that even low concentrations of gossypols inhibit the action of glutathione S-transferase, an enzyme widely distributed in the body for the detoxification of numerous foreign organic compounds. In rodents low concentrations also cause irreversible inactivation of another important enzyme, malate dehydrogenase, though this effect does not appear in human tests.

Dr. Lee said, "With further research into gossypol's biochemical mechanism and toxicology it may be possible to improve gossypol's effectiveness as a male contraceptive and at the same time eliminate the unwanted side effects."

Dr. Malling added that clinical reports in China show gossypol may be a very promising male contraceptive drug. It has proven to be reliable and relatively safe, provided that the dosage is kept at the anti-fertility level. Recent clinical studies by the Chinese showed that gossypol is an effective anti-fertility drug with a relatively low incidence of mild side effects. The fact that it occurs naturally in the cotton plant means that the supply is almost unlimited and would be very economical to produce. NIEHS is playing a role in learning about this drug through its research on the vulnerability of various biochemical systems of the body to environmental agents. ■

Gossypol researcher, Dr. Chi-Yu Lee, Laboratory of Environmental Chemistry and Dr. Heinrich V. Malling, right, Chief of the Laboratory of Biochemical Genetics, have begun to unfold the biochemical mechanism of a promising male contraceptive as a part of their biomedical research at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. NIH PHOTO #1696

Maternal Proteins May Protect Embryo from Immunologic Rejection

By Susan Johnson

NICHD investigators, Drs. Arun Agrawal, Anil Mukherjee and Rodney Ulane have discovered that two proteins produced by the mother may protect the mammalian embryo from immunologic rejection before and during implantation in the womb. NIH PHOTO #1697

A possible mechanism by which the embryo is protected against rejection by the mother's immune system during its first days in the uterus has been uncovered by scientists at the National Institute of Child Health and Human Developments (NICHD).

Transplants of tissue from one individual to an unrelated individual, or allografts, are invariably rejected, because the recipient's immune system recognizes the transplanted tissue as genetically foreign and mounts an attack against it.

The embryo is for all practical purposes an allograft. On its surface are proteins inherited from the father which are foreign to the mother. Theoretically, the mother's immune system should recognize the paternal proteins on the embryo and reject it. This does not normally happen, of course.

Many explanations for the success of this natural allograft have been proposed over the past 30 years, but none has been conclusively proven.

The NICHD investigators have discovtered that two proteins produced by the mother may protect the mammalian embryo from immunologic rejection before and during implantation in the womb. Uteroglobin, a protein synthesized by the uterus, crosslinks with the proteins on the embryonic surface, thereby hiding them from the mother's immune system. The crosslinking is catalyzed by the enzyme transglutaminase, a blood clotting factor. In the absence of transglutaminase, uterglobin cannot attach to the embryo.

The levels of both uteroglobin and transglutaminase in the uterus rise during early pregnancy. A deficiency of transglutaminase in the mother may result in spontaneous abortion, or rejection of the embryo, some experimental data suggest.

Using the rabbit as a model, the NICHD scientists incubated embryonic cells with maternal lymphocytes, the cells responsible for the immune response which leads to allograft rejection. As expected, the embryonic cells stimulated an immune response.

When the embryonic cells were pretreated with uteroglobin and transglutaminase, however, the maternal immune response was suppressed. Pretreatment with uteroglobin alone partially inhibited the immune response, but the scientists believe that trace amounts of transglutaminase in the incubation medium catalyzed the reaction. Pretreatment with transglutaminase alone did not suppress the maternal immune response.

This mechanism appears to protect the rabbit embryo up to about 9 days after conception, when the embryo is implanted in the womb. Only trace amounts of uteroglobin are detectable in the rabbit uterus after 9 days.

It is possible that other proteins or increased hormone levels in the uterus protect the embryo after this point. Also, the embryo is by then developing anatomical barriers, such as the placenta, between itself and the mother.

Further studies are needed to determine if uteroglobin plays an important part in maintaining human pregnancy, say the NICHD investigators. In addition, the experimental results obtained in their study must be reconciled with the fact that the embryo sometimes develops outside the uterus, as in the base of tubal or abdominal implantation.

Discovery of a mechanism by which the embryo is protected from immunological rejection by the mother may contribute to an understanding of allograft tolerance in general. More specifically, it may help researchers understand how cancerous cells escape rejection by the host's immune system.

This study was reported by Drs. Anil Mukherjee, Rodney Ulane, and Arun Agrawal at the annual meeting of the Society for Gynecologic Investigation in March, 1981. ■

Tissue Culture Test: New Hope for Brain Tumor Chemotherapy

By Maureen Miller
(student intern for the News Branch)

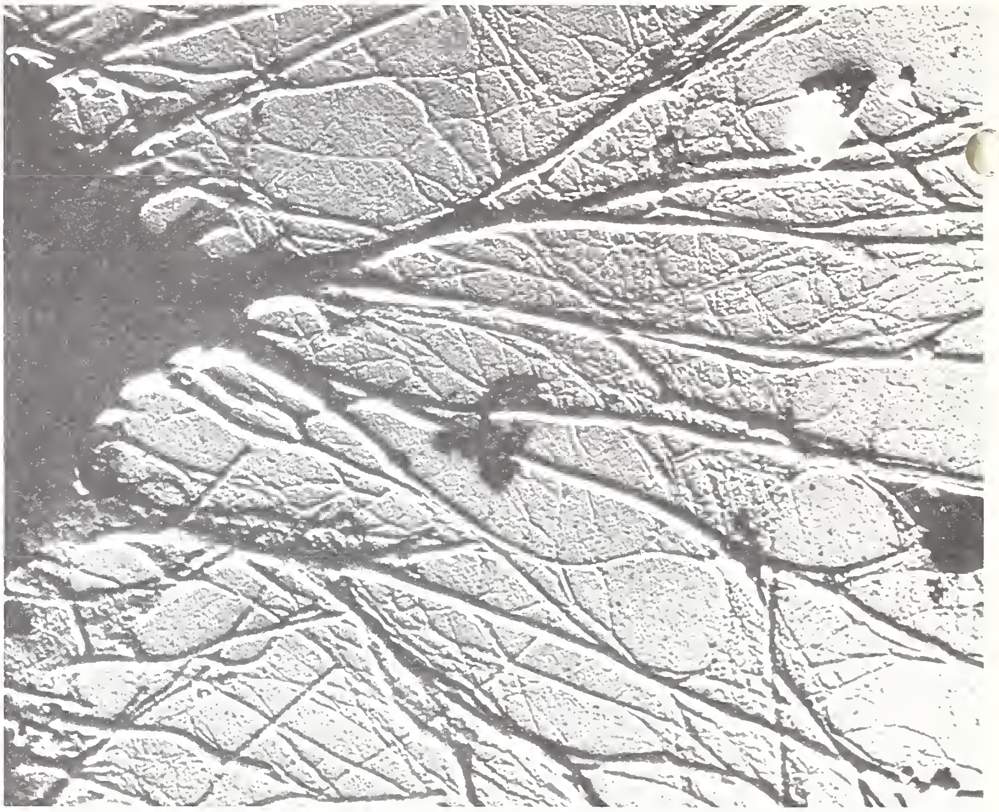
NIH researchers recently reported that laboratory testing of cancer cells from patients with brain tumors can predict their responses to anticancer drugs. Drs. Paul L. Kornblith, Barry H. Smith and their associates at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and colleagues from the Massachusetts General Hospital have found a positive correlation between the effects of BCNU—a chemotherapeutic drug—on cultured cells from cancer patients and on the patients themselves.

These test results indicate that physicians may use tissue cultures frequently in the future to determine the best chemotherapeutic drug for a brain tumor patient. Culture studies may also help scientists deepen their understanding of the growth of cancer cells, which may in turn open the door to new approaches in cancer therapy.

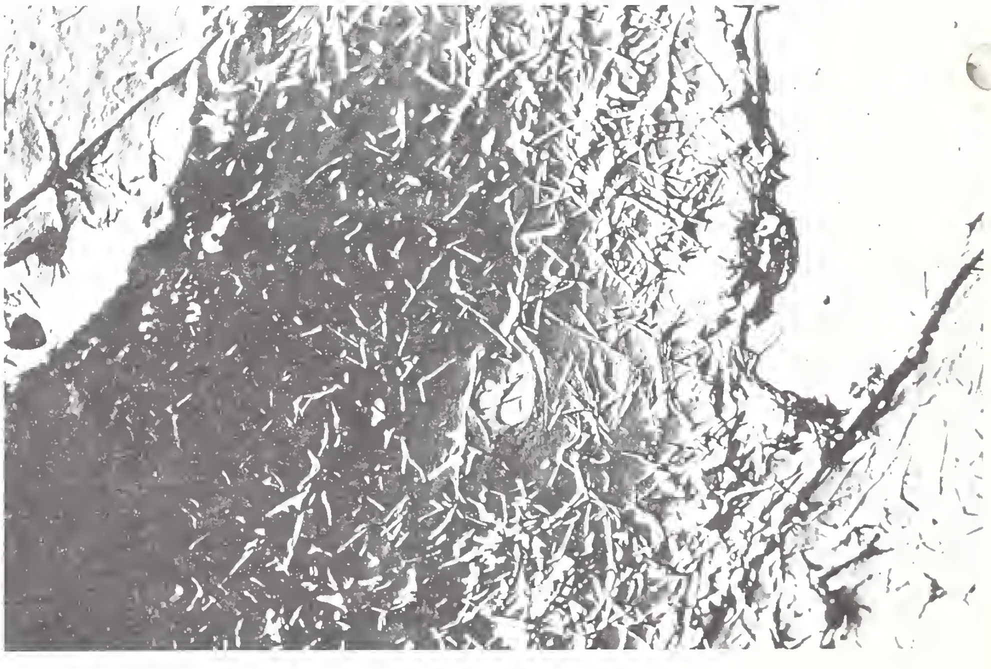
Kornblith and his associates obtained glial (brain tumor) cells from 58 patients. They treated the cells with different dilutions of BCNU and cultured them for one day. The next day, investigators took a count of cells which the BCNU had killed. The drug destroyed a significant number of cells in 42 of the 58 cultures (72 percent).

In the second phase of the study, investigators compared the same data to the responses of 14 of the 58 patients given BCNU. The 14 patients were chosen because they had all been through a complete therapy program. The program included postoperative radiation therapy, two or more doses of BCNU or related compound, CCNU, and two or more postoperative tumor scans at three-month intervals to detect any changes in tumor size.

For the 14 patients, tumor cell cultures of nine responded to BCNU, while cultures of five did not. Researchers then correlated these data with the data from patient therapy programs that had been completed. The results showed that tumor size increased in all five patients whose tumors did not respond to BCNU in the *in vitro* (outside of the body) test. Of the patients whose cultures did respond to BCNU, tumor size decreased in six of them over a span of a year and half to four years. Tumor size increased in two of the other three patients and remained the same in one.



Certain features of malignant tumors in culture are useful in grading their degree of malignancy. Processes with multiple branching occur in well-differentiated brain tumors.
NIH PHOTO #1698



Features of a highly malignant brain tumor known as an astrocytoma in culture. Astrocytomas comprise the group of human brain turmors in which predictive information is most crucial. They range from totally benign tumors to the most rapidly growing human cancers.
NIH PHOTO #1699

The correlation between laboratory and clinical responses to BCNU strongly suggests that the *in vitro* test can predict how patients will respond to chemotherapy. It can then be used to evaluate if, and what kind of chemotherapy doctors should prescribe for a patient. The major advantage of the *in vitro* test, then, is the ability to study each patient's tumor, which is unique. Researchers now realize that different patients may have the same type of tumor, but each person's tumor has different biological properties, which cause it to react to chemotherapy in a unique manner.

Researchers must verify Kornblith's study by conducting further studies that are based on larger sample sizes. In future studies, they will determine the desired confidence level on *in vitro-in vivo* (within the body) correlations, and what type of *in vitro* tests best predict clinical response.

Investigators have established clear parameters for distinguishing non-malignant tumor cells from malignant tumor cells, and grades of malignancy for the latter. They have not, however, been able to clearly account for biological differences in similar types of tumor cells from person to person. Many natural factors such as metabolism, hormones, nutrition and immunologic characteristics contribute to biological differences in tumor cells among individuals. These characteristics similarly determine the patient's response to chemotherapy and future studies will have to test the remaining variables to tailor chemotherapy optimally for individual patients.

Several investigators have compared the effectiveness of BCNU to its relative, CCNU. While they have not found any significant differences between the two compounds, some investigators cite a few advantages of CCNU. It can enter the brain tissue a little more easily, and it can be given orally, eliminating the need for a hospital visit for each dose of chemotherapy. Kornblith and associates opted to use BCNU in this study, however, because it is more soluble in water solution which makes it more suitable for *in vitro* testing.

To summarize, although more extensive studies are needed to verify that *in vitro* testing can accurately predict clinical response in patients, Kornblith's study indicates several promising avenues. First and foremost is the potential value of the *in vitro* test to the individual brain tumor patient. Secondly, the long-range benefits of *in vitro* testing may well include new approaches to cancer therapy in general, as scientists increase their understanding of malignant cells. ■

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News&Features from NIH

September 1981

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Spotted Fever: A Record Year Draws to an End **p. 12**

NICHD Project Takes a New Look at the Cervical Cap **p. 3**

Your Gums May Be in Trouble Without Vitamin C **p. 13**

DES Proves to be an Effective Research Tool in Studying the Body's Immune System **p. 10**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

NIH PHOTO #1700

News&Features
from NIH

September 1981

Rocky Mountain Spotted Fever, a disease transmitted by wood ticks, is on the increase, and is no longer confined to the Rocky Mountain area. According to NIH researchers, new vaccines are in the works, but further testing is needed to prove their effectiveness for mass vaccination.

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After eight years, researchers studying women using oral contraceptives have found that these women do not face an increased risk of death, and that they do not seem to have a higher incidence of breast cancer or benign ovarian tumors. It was also noted that the risk of high blood pressure seems lower than previously reported.

See page 11

Neurologists from NIH travel throughout the world to find clues to baffling brain disorders such as amyotrophic lateral sclerosis, Huntington's disease, and other neurological disorders. With the help of animal models and the information gathered from various diseased populations, scientists are hopeful of someday finding the key to many of the most mysterious neurological disorders.

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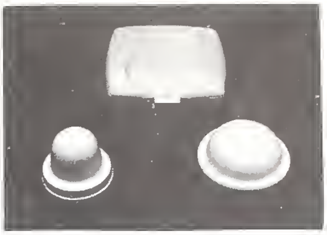

Researchers are studying a new birth control device that really isn't so new. The cervical cap, first described over 100 years ago is once again being considered as a form of contraception for women who do not wish to use the Pill or the IUD.

Similar to the diaphragm, but smaller, the cervical cap acts like a barrier and prevents sperm from entering the uterus. It fits securely, blocking only the cervix, and reportedly does not become dislodged as the diaphragm often does.

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Unusual Mole May Identify Families Prone to Malignant Melanoma

By Florence Karlsberg

Scientists at the National Cancer Institute (NCI) and the Pigmented Lesion Clinic, Hospital of the University of Pennsylvania, have identified a new syndrome, the Dysplastic Nevus Syndrome, in members of families predisposed to malignant melanoma. They have identified an unusual mole that represents a marker of increased risk for melanoma in melanoma-prone families. These moles have also been identified in patients with sporadic (non-familial) melanoma, suggesting that these precancerous lesions are more prevalent in the general population than previously estimated.

Malignant melanoma is a type of cancer that originates in the pigment-forming cells of the skin. In those individuals with the Dysplastic Nevus Syndrome, the pigment-forming cells in moles undergo abnormal cell changes that predispose them to melanoma. People with this syndrome have been found to have dysplastic (abnormal in size and shape) moles, a small fraction of which progress to malignant melanoma. Surgical removal of the most abnormal of these moles can prevent progression to malignancy in high-risk individuals.

Dr. Mark H. Greene and coworkers in the Family Studies Section of NCI's Environmental Epidemiology Branch study cancer-prone families to identify mechanisms of cancer susceptibility. They began studying the melanoma problem in the family setting because the number of new cases each year has been increasing both in the U.S. and internationally, and melanoma seems to occur more frequently in certain families. In addition, the chances of surviving melanoma have improved due to advances in our understanding of the stages of the disease.

These observations provided an impetus to search for clues to melanoma susceptibility. In April 1976, Dr. Greene's group evaluated a melanoma-prone family of 25 members with four known melanoma patients (one deceased). The three surviving melanoma patients and a number of their healthy relatives were found to have a very unusual pattern of moles on their skin.

Larger and more numerous than ordinary moles, these lesions had irregular outlines and pigmentation and seemed to be found all over the skin, including areas where ordinary moles are usually not seen, such as the scalp and buttocks.

One family member had a previously undiagnosed malignant melanoma. This tumor was found to be an early melanoma curable by surgical removal. This patient is now alive, well, and free of melanoma five years later.

During 1977-78, the study was expanded to include six additional families whose members were found to have the same unusual mole pattern as the first family. Microscopic examination of pigmented moles removed from family members showed a disordered, faulty growth in the pigment-forming cells (melanocytes). Additional family members with unusual moles have been diagnosed with early melanoma since the study began.

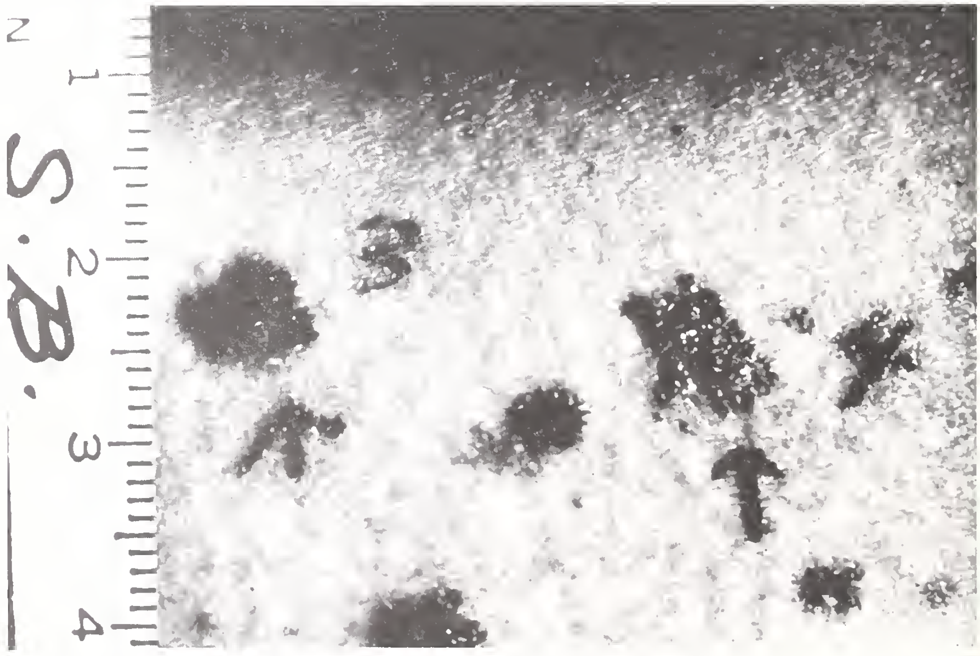
Detailed analyses have confirmed that these lesions are unusually susceptible to malignant transformation. All family members whose melanomas were found in the course of the study are still alive, probably because the melanomas were of the early type and relatively small. Careful monitoring of persons with these unusual moles could lead to a decrease in deaths from melanoma, now averaging 5,000 annually in the United States.

An estimated 14,300 new cases of melanoma will occur in 1981. Its incidence has doubled during the past few decades and continues to increase on a worldwide basis. Although the evidence is as yet uncertain, this upward trend may be related to changes in clothing habits and recreational sun exposure.

Up to 10 percent of melanoma patients are members of melanoma-prone families. An estimated 50 percent of the melanoma-prone family members have these unusual moles and are believed highly susceptible to the development of a melanoma in the abnormal mole. The scientists have also reported the occurrence of these abnormal moles in melanoma patients with no family history of melanoma, an observation that has been verified by other investigators. Although no data exist on how many people in the general population may have these atypical moles, a recent study has suggested that this syndrome may be more prevalent than previously estimated.

In addition to a set of written guidelines for early detection and prevention of melanoma, Dr. Greene and his colleagues have developed a series of educational video-cassettes for family members and physicians. These materials illustrate the characteristics of unusual moles (dysplastic), the melanoma warning signals, principles of skin self-examination, ways to minimize sunlight exposure, and recommendations for daily health care.

At the University of Pennsylvania the research was conducted by Wallace H. Clark, Jr., M.D. and David E. Elder, M.D. The NCI collaborators include Margaret A. Tucker, M.D., Kenneth H. Kraemer, M.D., and Mary C. Fraser, R.N., M.A. ■



The photo above shows the unusual pigmented lesions of a 26-year-old white female who has had two primary malignant melanomas. Her mother has had one melanoma.

The nevi are large, have an irregular border and are variably pigmented with shades of brown, tan, pink, and black. Lesion #4 is a typical dysplastic nevus and lesion #3 was clinically suspicious for early melanoma because of the black pigment along its upper border. The biopsy showed that the suspicious mole was not malignant but a severely dysplastic nevus.

NIH PHOTO #1701

The Cervical Cap—a Birth Control Device over 100 Years Old—is Being Considered Again

By Maureen Gardner

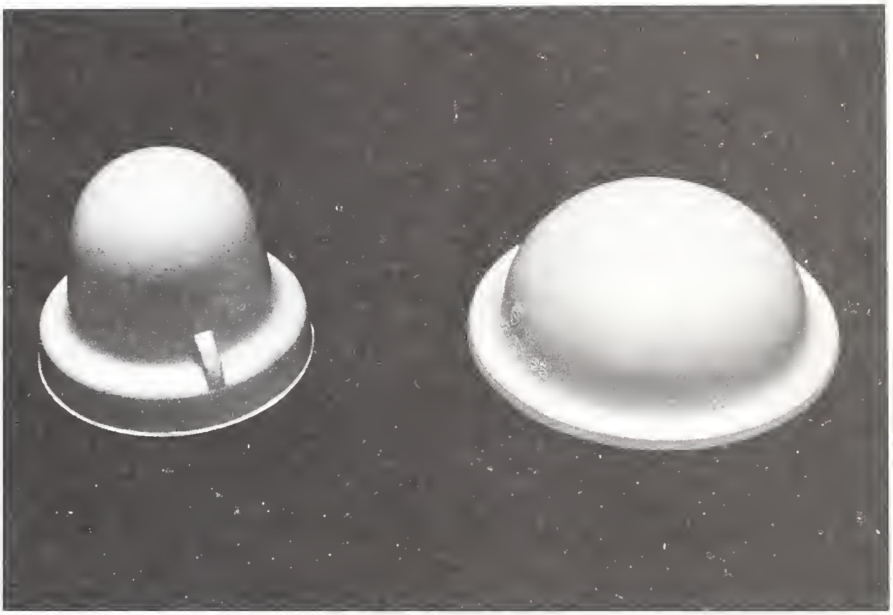
A birth control device for women which was first described in medical literature more than 140 years ago will be studied in three research projects supported by the National Institute of Child Health and Human Development (NICHD). It may not be a new idea in contraception, but the cervical cap, a "barrier" device similar to the diaphragm, has received renewed interest from many women who wish to avoid the health risks associated with the Pill and the IUD.

Like the diaphragm, the cap fits in the upper vaginal canal and acts as a barrier that holds contraceptive cream or jelly and prevents sperm from entering the uterus. Usually made of plastic or rubber and shaped somewhat like a thick thimble, the cap is smaller in diameter than the diaphragm and more rigid. Unlike the diaphragm, the cap is held in place by suction, and it blocks only the cervix, or opening to the uterus, as opposed to the entire upper vaginal canal. A properly fitted cap is reportedly less likely to become dislodged during intercourse than is the diaphragm. A drawback of the cap is that it is more difficult than the diaphragm to insert and remove.

The cap's main advantage over the diaphragm, claim its proponents, is that it can offer contraceptive protection for days at a time, compared with a matter of hours for the diaphragm. Although it has been used widely in Europe, the cap is not currently available in this country except to women participating in research studies.

NICHD-supported research on the design of cervical caps is underway at the Brigham and Women's Hospital in Boston, Massachusetts, while separate projects by the Los Angeles Regional Family Planning Council and the International Fertility Research Program in North Carolina will evaluate the safety, effectiveness, and popular acceptance of several kinds of caps.

At the Brigham and Women's Hospital, doctors are working to design an improved cervical cap. They began by studying the characteristics of the cervix itself, and have found it to be far more mobile and changeable than previously described. Although these factors make it more difficult for the cap to stay in place, the investigators believe these problems can be overcome.



The cervical cap (left) is smaller in size than the diaphragm, fits securely by suction and does not have to be removed for several days. NIH PHOTO #1702

The biggest area in question about the cap is its effectiveness. Up to now, little research has been performed on this topic, and conflicting results have been obtained from the few minor studies that have been done. The largest of the three NICHD-supported projects, to be run by the Los Angeles Regional Family Planning Council, will focus mainly on the effectiveness of two kinds of cervical caps as compared with standard diaphragms.

The 4-year multicenter, multimillion-dollar trial began in July 1981. In the first two years of the study, four health centers will enroll a total of 2,400 women who will be randomly assigned in groups of 800 to the diaphragm or one of the two caps: the Prentif Cavity Rim Cap or the Vimule Cap. Throughout the study, the women will be followed to compare the pregnancy rate, the risk of any adverse effects, and the discontinuation rate for each of the three devices.

The Los Angeles investigators will also look at the question of how long the caps can be safely worn. Although cap manufacturers recommend wearing the cap no longer than 24 hours, many women's health groups contend that it can be worn safely for 3 to 7 days. The study will initially determine whether the caps can indeed be worn for 7 days without significant side effects.

The third cervical cap project, to be conducted by the International Fertility Research Program, will test a newly developed model that is very different from most currently available caps. Ironically, this recent version has something in common with the first cervical caps described in 1838: custom fit. Unlike its prototype, however, the "Contracap" has a one-way valve that permits menstrual and cervical fluids to exit while preventing sperm from passing through. According to its developers, the Contracap can be worn continuously and does not need spermicide to be effective.

For each of the 300 women in the 18-month study, researchers will make a cast of the cervix to create a model (this takes only 5 minutes); then they will shape a flexible copolymer material into a Contracap. As with the Los Angeles study, the investigators will be looking at the safety, effectiveness, and the ease of use of the caps. Once these studies and others are completed, the information gained will help to guide decisions on whether the cervical cap, in any form, will be marketed in the United States. ■

Aging Institute Highlights Senility Research

By Marian Emr

Of the 25 million people over 65 in the United States, as many as 3 million experience what is to them a disturbing loss of memory. Of these, 1 million are victims of true senile dementia, the progressive decline in intellect that most people call "senility."

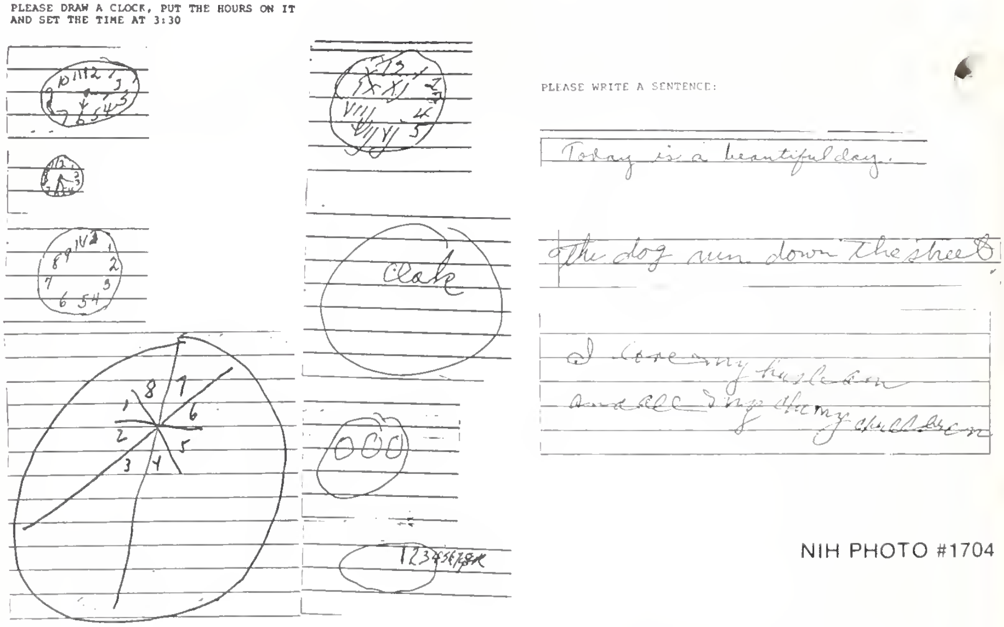
Senile dementia of the Alzheimer's type (SDAT), a relentless and devastating disorder, is the most common incurable form of "senility." In SDAT, changes in the nerve cells of the cerebral cortex (outer layer of the brain) result in the death of a large number of cells.

Alzheimer's disease was first described in November of 1906 at a meeting of the South West German Society of Alienists when Alois Alzheimer, a German physician, recounted the story of a 51-year-old patient. The woman's problem began with loss of memory and disorientation, later was complicated by depression and hallucinations, and eventually resulted in severe dementia and death.

Upon death, the patient's brain was found to show severe atrophy (shrinkage) and the cerebral cortex was marked by a clumping and distortion of fibers in the nerve cells. Alzheimer called these jumbles of filaments neurofibrillary tangles, and they have since become the hallmark of Alzheimer's disease. In studies which followed, researchers discovered other anatomical changes in Alzheimer's disease including neuritic plaques, degenerating nerve endings that disrupt the passage of electro-chemical signals. Because of Alzheimer's findings of this disorder in a middle-aged woman, and other reports which followed, Alzheimer's disease is classically considered to be a presenile (pre-old age) form of dementia. Nonetheless, recent studies show identical anatomical changes in both Alzheimer patients and the majority of elderly "senile" patients—suggesting that senile dementia of the Alzheimer's type is far more prevalent than the presenile form of Alzheimer's disease.

In the early stages of the disease, the SDAT victim typically has problems with learning, memory, and attention, which often leads to misplacing items, taking longer to complete tasks, or having trouble following a conversation. As the disease progresses over time, the patient becomes more disoriented, exhibits errors in judgment and difficulties in reasoning and thinking, and speech may be affected.

Patients with Senile Dementia of the Alzheimer's Type sometimes notice that their writing abilities decrease as the disease progresses. NIH PHOTO #1703



PLEASE DRAW A CLOCK, PUT THE HOURS ON IT AND SET THE TIME AT 3:30

Clock
12345678

PLEASE WRITE A SENTENCE:

Today is a beautiful day.

the dog run down the street

I love my husband and all of my children

NIH PHOTO #1704

Personality changes often accompany mental changes in later stages of the disease, with patients showing signs of paranoia, depression, agitation, restlessness, violence, or apathy. In severe cases, some patients become unable to care for themselves and special settings with professional staff and full-time care may be required.

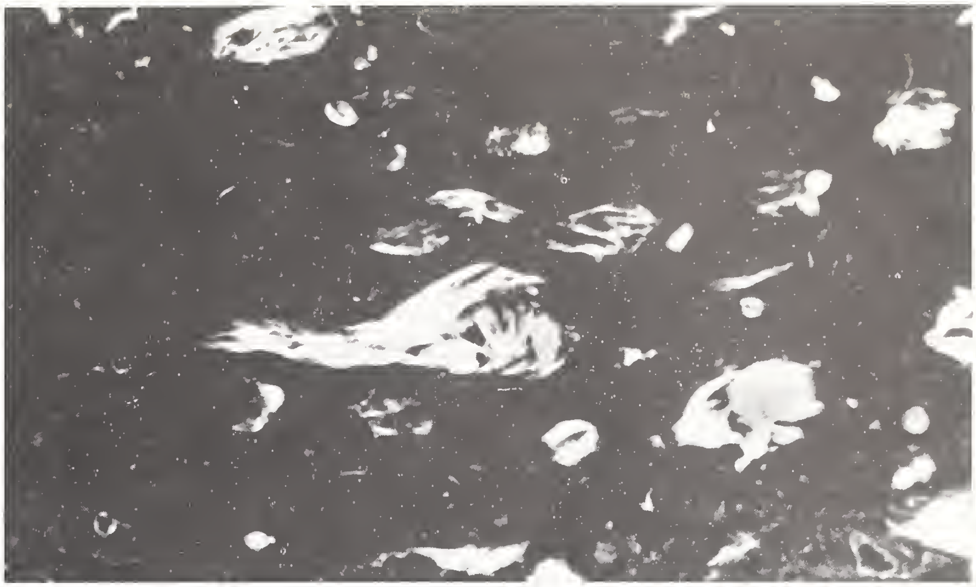
Given the current state of our knowledge, SDAT is progressive and incurable, but there is much that can be done to help the victim live as full and functional a life as possible for as long as possible. Proper nutrition is important, as is encouraging the patient to maintain daily routines, physical activities, and social contacts. Stimulating the individual by supplying information on the time of day, place of residence, and what is going on in [illegible] immediate environment and in w[illegible]d events, encourages the use of skills and information which remain.

Such memory aids as a very visible calendar, lists of daily activities, written notes about simple safety measures, and labeling of commonly used items can help in day-to-day living. Handrails, safety locks on doors and cabinets, and smoke alarms can all make a home environment a safe place in which to be forgetful. Careful use of drugs can lessen agitation, anxiety, and depression, and improve sleeping patterns if this is necessary.

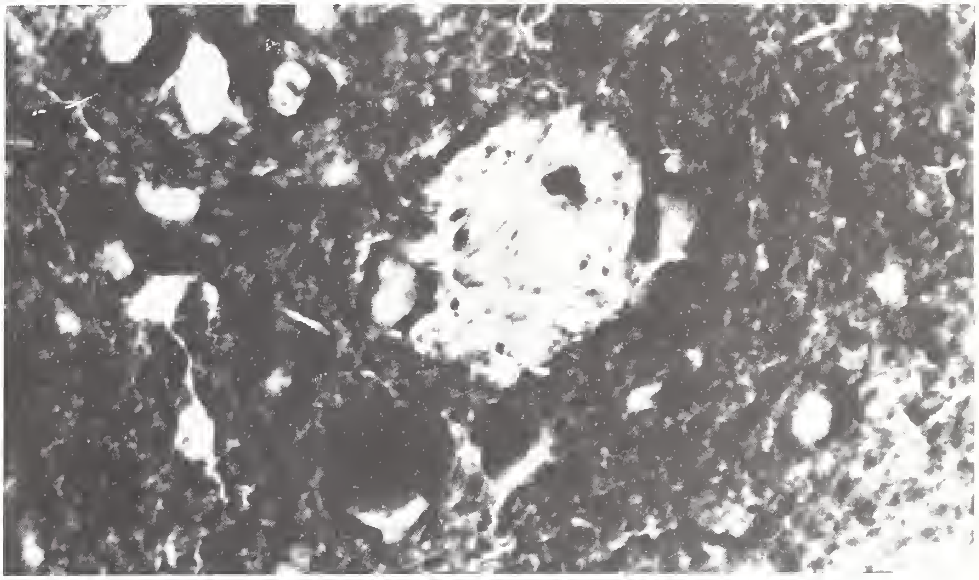
Research studies looking towards the cure and prevention of all forms of senile dementia have been in progress since the National Institute on Aging (NIA) was established in 1974. To provide a fundamental base for this research, epidemiologists at the Institute are attempting to determine who the victims of SDAT are and if there is an "at risk" group who might be most susceptible to this disorder. Jacob Brody and the staff of the Institute's Epidemiology, Demography, and Biometry program have outlined a strategy to identify and study noninstitutionalized persons with early or mild cases of senile dementia. In one community-based survey of mental illness, researchers will attempt to "sort out" SDAT victims who have remained outside of institutions. In a second study, the group will try to develop a more accurate picture of the natural progression of the disease and attempt to determine specific risk factors.

Another focus of the NIA's plan for the prevention of SDAT is aimed at developing a better understanding of the cause or causes and mechanisms of the disease. To date, the most exciting findings show that patients with this disease have a marked reduction in a specific chemical in the areas of the brain associated with memory. Attempts to stimulate the reduced chemical activity have been modestly successful and show convincing evidence that we are closer to the possibility of treatment then ever before.

While there is a great deal of excitement about exploration of neurochemical changes in SDAT, the NIA's extramural research program on the neurosciences of aging, directed by Zaven Khachaturian, supports studies on as many as four other leading theories as to what causes this disease. The theories are as diverse as the disciplines of the experts pursuing them, including toxicology, immunology, genetics, and virology. Their findings come in the context of scientific achievements of the past few decades: 1) findings which first began to separate normal brain aging from age-related disease in the brain; 2) findings which linked the symptoms of dementia with specific pathological changes in the brain; 3) the availability of technology which has revolutionized our abilities to study brain structure and function and to diagnose disease in its earliest stages; and finally, 4) ongoing studies to develop a clearer understanding of normal brain function and what happens to the brains of SDAT victims.



Tangles are well named. The white areas that look like twisted bits of yarn are neurofibrillary tangles, magnified in this view of the cortex of a patient with Alzheimer's disease.
NIH PHOTO #1705



A single neuritic plaque is shown at the center of this magnified view of the cortex of an Alzheimer's disease brain. The dense white area in the center is the core of the plaque, composed of amyloid. Surrounding the core are wisps of amyloid material and degenerating bits of nerve fibers. Two neurofibrillary tangles can also be seen: one at center top; the other at the upper right. NIH PHOTO #1706

To augment our knowledge of normal and abnormal changes in the aging human brain—and to develop a foundation for effective treatment of senile dementia—the NIA has initiated a long-term research attack on SDAT at its Gerontology Research Center in Baltimore. In the first step of this intensive effort, already underway, Stanley Rapoport and his staff are examining regional brain metabolism in healthy individuals to see how this can be linked with changes in their abilities to perceive, think, and remember over time. In the second stage of Rapoport's long-term plan, the information from this study will be used to evaluate brain activity in patients with SDAT.

For more information on research programs on senile dementia of the Alzheimer's type, contact the National Institute on Aging, NIH, Building 31, Room 5C35, Bethesda, Maryland 20205, or the National Institute of Neurological and Communicative Disorders and Stroke, NIH, Building 31, Room 8A06, Bethesda, Maryland 20205. ■

Photos courtesy of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the Albert Einstein College of Medicine of the Yeshiva University and the National Institute on Aging, Baltimore Campus, (NIA).

Artificial Fat May Be a Key to Lower Cholesterol and Healthier Lives

Researchers at the University of Cincinnati are testing a synthetic, artificial fat called sucrose polyester (SPE) which appears to significantly lower elevated cholesterol levels, considered to be a major risk factor in heart disease. This fat product also holds potential promise as a therapeutic agent in weight reduction programs and in preventing colon cancer, which has been linked to high fat diets.

SPE is synthesized from sugar (sucrose) and fatty acids, forming a compound that cannot be absorbed by the body.

Studies conducted at the University of Cincinnati General Research Center by Dr. Charles Glueck, chief investigator, and his colleagues, Drs. Fred Mattson and Ronald Jandacek indicate that SPE reduces high blood cholesterol levels in healthy, nonobese male subjects by 16 to 18 percent. SPE appears to reduce the absorption of both cholesterol present in foods eaten with it and cholesterol which has entered the intestine in the bile.

SPE has tremendous promise for preventing atherosclerosis, which is a form of hardening of the arteries, according to Glueck. Atherosclerosis has been linked to elevated levels of serum cholesterol. Cholesterol, an essential tissue component of organs, can form plaques and adhere to the interior walls of arteries, stopping blood flow, especially in coronary vessels.

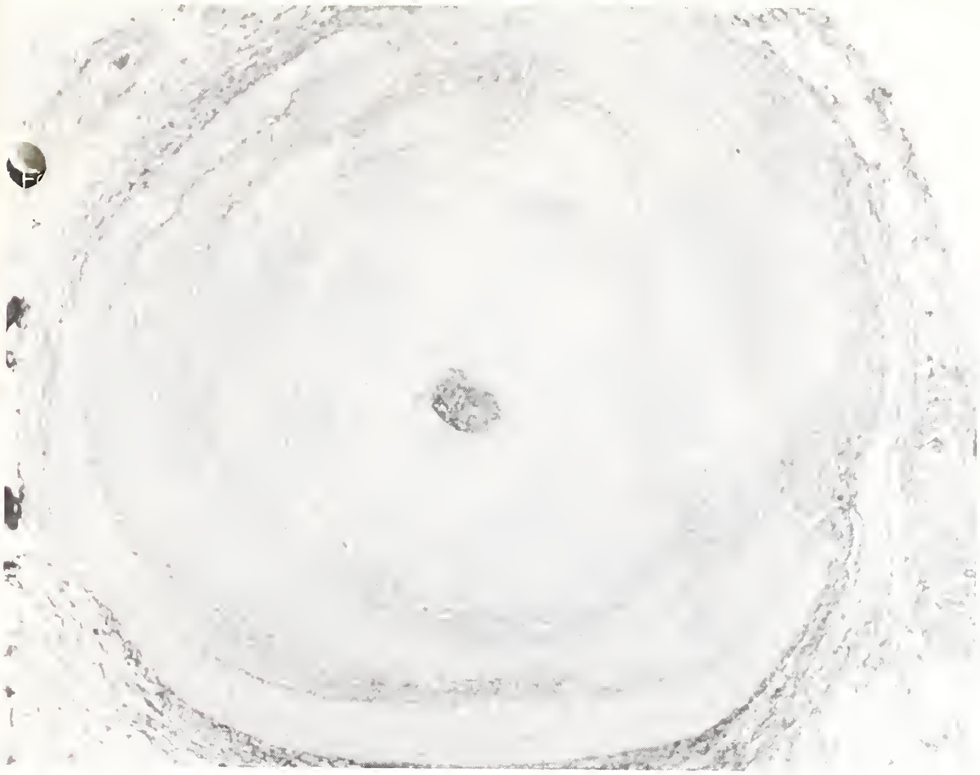
The researchers found that the cholesterol from food and bile binds to SPE on its way through the intestine and is carried out of the body as waste products. Each gram of SPE eaten results in a 1.3 percent increase in excretion of cholesterol and its conversion products (chemicals or by-products formed from bacterial action on cholesterol).

The effects of SPE on cholesterol absorption in the intestine were also studied in 29 adult African green monkeys at Bowman Gray School of Medicine of Wake Forest University. Dr. Richard W. St. Clair and his colleagues found, as in humans, that the effect of SPE was greater in certain individual animals than in others. The investigators noted that the animals with excessively high concentrations of cholesterol respond most dramatically to SPE with a sharp reduction in their cholesterol levels. This effect was due mainly to a decrease in low-density lipoproteins, which are the chief carriers of cholesterol in plasma. SPE had little effect on high-density lipoprotein cholesterol.

In addition, SPE has the unique property of not being absorbed into the body, which could help individuals who must lose weight, and yet find it difficult to give up things like butter, mayonnaise and heavy cream. It can be made to mimic ordinary food fats in texture, smell and taste. But unlike these food fats, it is not broken down in the intestines, and therefore is not absorbed into the body. Ordinary fats are digested by lipase enzymes in the intestine into products that are absorbed into the body. Every gram of SPE substituted for a gram of conventional fat saves 9 calories, according to Glueck. However, SPE's use in we reducing is still speculative.

This artery is completely wide open and clear of disease.

NIH PHOTO #1707



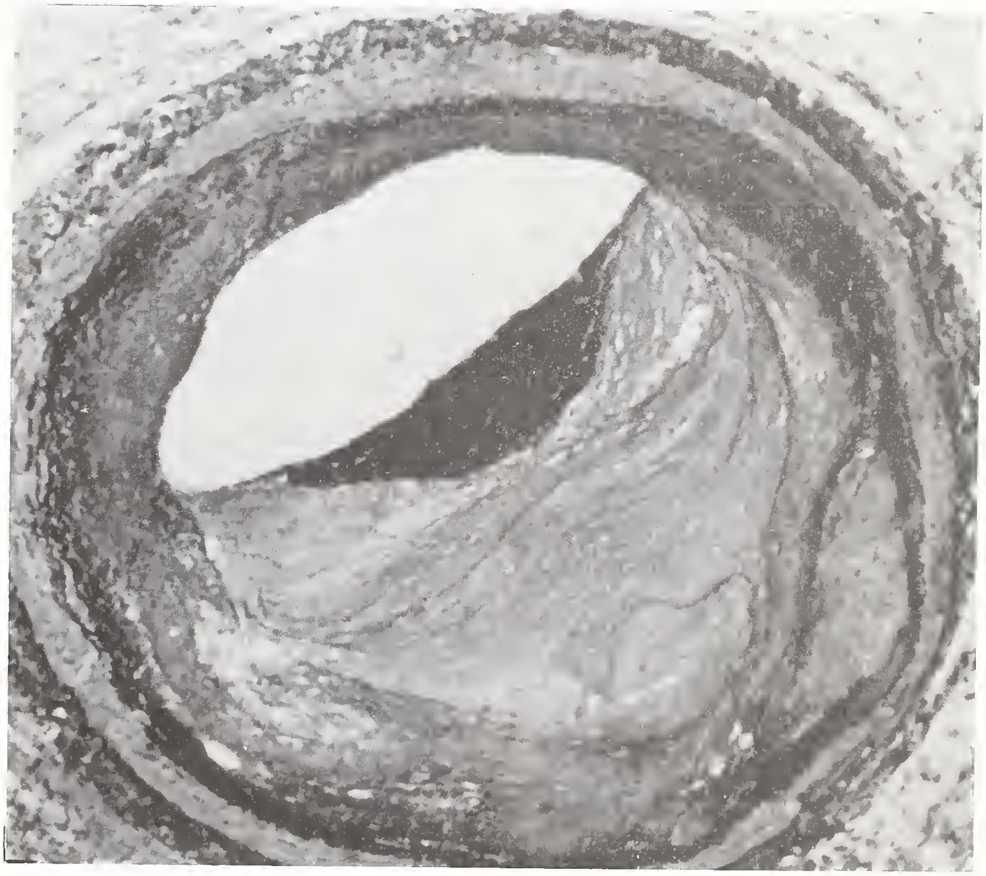
This artery is completely blocked. The dark area in the center is a thrombus or clot. The rest of the gray mass is atherosclerotic plaque. NIH PHOTO #1708

The use of SPE in preventing colon cancer has not been proven or tested, however, studies have revealed that diets high in cholesterol and total fats are associated with this type of cancer.

SPE has no known side effects, but it does have one possible drawback, Mattson said. It appears to interfere with the absorption of fat soluble vitamins, especially Vitamins A and E. Therefore, individuals who take SPE may have to supplement their diet with these vitamins.

SPE may be marketed within two to three years pending approval from the Food and Drug Administration. It would probably start out as a prescription drug, because of its powerful cholesterol-lowering effect. With further testing, it may have potential as a zero-calorie fat substitute to be used in weight reducing programs.

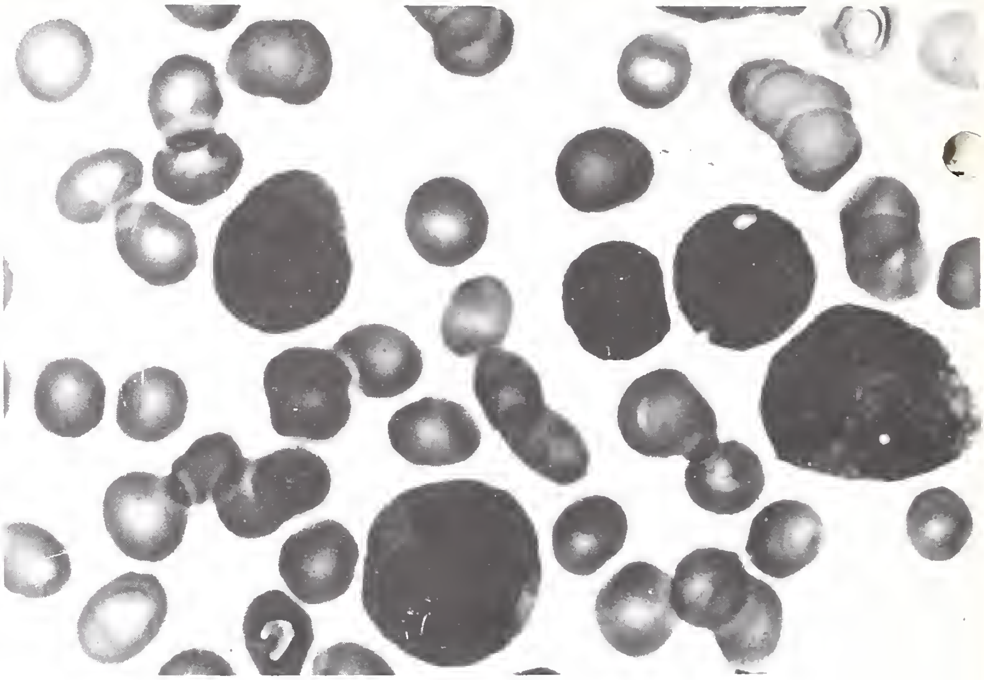
These studies were funded by the National Heart, Lung, and Blood Institute (NHLBI) and the clinical applications were carried out at the University of Cincinnati General Research Center, a spe[illegible]l clinical investigation hospital unit [illegible]ded by the Division of Research Resources (DRR). ■



This artery is partially blocked by an atherosclerotic plaque with an overlaying thrombus (shown in the dark area). NIH PHOTO #1709

Scientists Question Use of Transfusions for Patients with AML

By William Sanders


The white blood cells are stained in this blood sample from a patient with chronic leukemia.
NIH PHOTO #1710

Daily transfusions of granulocytes (a type of white blood cell) are of no value in protecting patients with acute myelogenous leukemia (AML) against infections during chemotherapy, according to results from a clinical trial supported by the National Heart, Lung and Blood Institute (NHLBI).

In AML and certain other "stem cell leukemias," immature white blood cells are produced at an accelerated rate. They accumulate rapidly in bone marrow, where they impede production of red blood cells and platelets; and they often invade other tissues, particularly the liver, spleen, and lymph nodes. Most victims of these diseases are young children.

These forms of leukemia are usually fatal if left untreated, but remissions of varying duration may be achieved in most patients with intensive chemotherapy. Unfortunately, the massive destruction of white cells plus the associated bone marrow depression resulting from the chemotherapy reduce these patients' defenses against infections. These patients may, therefore, not respond adequately to treatment with antibiotics.

The NHLBI-supported study investigated whether prophylactic transfusions of human granulocytes might provide some degree of protection against the infections that are prone to occur following chemotherapy. The subjects were 102 patients with AML, all found to be free from infection when chemotherapy was begun. Patients were eligible for entry into the study when the concentration of blood neutrophils fell below an acceptable level. Over the 28-day period of study, 54 of these patients received daily transfusions of granulocytes in conjunction with their chemotherapy; the other 48 did not. Treatment was otherwise comparable in both groups of patients.

The transfusion of granulocytes did not reduce the overall incidence of infections—which occurred in 46% of the transfused patients and 42% of the controls—but did reduce the proportion of patients who subsequently developed bacterial septicemia (invasion of the bloodstream by pathogenic bacteria), which occurred in 9% of transfused patients versus 27% of the controls.

Of the patients given transfusions of granulocytes, 72% developed reactions, which included increases in temperature, shaking, chills, and respiratory difficulties (dyspnea or wheezing). These circumstances forced transfusions to be interrupted in 15% of the patients and terminated altogether in 11%. A high proportion of transfused recipients than control subjects developed pulmonary infiltrates (57% versus 27%, respectively). Though the cause of these infiltrates was not clearly defined in all circumstances, they were definitely a factor adversely affecting survival. Whereas 35% of all patients with pulmonary infiltrates died during the 28-day period of study, only 5% of patients without infiltrates did not survive.

Overall mortality during the study was higher among patients receiving infusions of granulocytes (22%) than among controls (13%), although the difference did not reach statistical significance. Two-thirds of all deaths were the result of infections, which granulocyte transfusions apparently did little to prevent.

The only obvious benefit of granulocyte transfusions in the treatment of AML was some reduction in the risk from bacterial septicemia. This benefit appears to be heavily outweighed by the substantial risk of transfusion reactions and other complications that may accompany such therapy. From the results of this study, the investigators conclude that prophylactic transfusions of granulocytes cannot be advocated as standard therapy during chemotherapy to induce remissions in patients with AML.

The centers and members of their medical staffs who participated in this study are: University of Iowa, Drs. R. Strauss, L. Maguire, D. Stump, M. Goedken, C. Tipping, J. Koepke, and J. Thompson; University of Minnesota, Drs. J. McCullough, C. Bloodfield, D. Hurd, B. Peterson, P. Warkentin, and W. Krivit; UCLA, Drs. R. Gale, D. Winston, W. Ho, M. Tesler, K. Baroni, L. Young, and M. Territo; Washington University, Drs. G. Herzig, W. Miller, S. Staggs, L. Dumler, and D. Ratliffe; Coordinating Center (U. Minnesota), Drs. J. Connett, G. Bartsch, Grina, D. Balestracci, and K. Dunlap.

Cancer patients are sometimes given chemotherapy treatment as outpatients in the Clinical Center, the NIH's research hospital, located in Bethesda, Maryland.
NIH PHOTO #1711

This report was in a recent issue of the *New England Journal of Medicine.* ■

New Treatment Breaks Cycle of Chronic Hepatitis B Infection

By Joan Hartman

A team of physicians has protected newborn infants from becoming lifelong carriers of hepatitis B virus (HBV), a potential precursor of serious liver diseases and liver cancer.

All the mothers of the newborns in the federally-funded study were chronic carriers of the virus. They also carried a piece of the virus known as the HBe antigen. Nearly all chronic HBe antigen carriers infect their infants with the HB virus within a few months of birth, and 85 to 95 percent of infected babies become chronic carriers themselves.

They may never have outward signs of disease, but they can still infect others. More than one-third of carriers develop chronic liver diseases, and they have a much higher risk than average of getting cancer of the liver—up to 273 times that of noncarriers.

Evidence that offspring of chronic HBV carriers need not go through life with the virus and its associated risks comes from a study supported by the National Institute of Allergy and Infectious Diseases and the Food and Drug Administration's Bureau of Biologics.

In the study, high risk infants received three injections (at birth, 3 and 6 months) of a human blood component rich in the immune system's natural defenders against the virus—hepatitis B antibodies. The extract is called hepatitis B immune globulin (HBIG).

The results were dramatic. Although three-fourths of the infants developed an infection, only one-fourth became chronic HBV carriers.

A second group of newborns received on injection of HBIG at birth, then two injections of a placebo, an inactive substance that lets researchers compare different treatment groups. The single dose of HBIG offered some protection: only half the infants became chronic carriers.

A third group received three placebo injections. As could be expected, over 90 percent became chronic HBV carriers. All the infants were watched for at least 15 months.

Timing of the initial dose appeared to be critical. If given more than 48 hours after birth, HBIG apparently fails to prevent development of the carrier state, the study indicated.

Hepatitis B virus infects millions of people around the world, but the chronic carrier rate varies from country to country. It is as high as 15 percent in some developing countries, with the rate climbing to 30 percent in population subgroups of those nations. Thus, the possibility is significant of reducing deaths from liver diseases and liver cancer by controlling chronic HBV infection.

In the United States the chronic carrier rate is very low—1 percent or less—but here, too, subgroups run greater risks. Pregnant women with active hepatitis B infection are one example. Also, Asians living in the U.S. have higher carrier rates than the overall population. Approximately 4 to 6 percent of all Chinese-American mothers will transmit the HB virus to their newborns. The vast majority of these babies will become carriers themselves, with associated risks for chronic liver diseases, liver cancer and for passing the virus to others.

In the study, HBIG often did not protect the infants from HBV infection, but it did delay its onset. Over half the babies who received three doses of HBIG were more than nine months old before infection appeared. But simply delaying the initial infection may be protective. Fewer of the treated infants who were seven months of age or more when infection first appeared became chronic carriers than did those babies who became infected within their first six months of life.

The investigators suggested that women at high risk of transmitting the virus, as indicated by ethnic group or history of HBV infection, should be screened routinely during pregnancy to determine if they are chronic carriers. If tests are positive, protective treatment with HBIG could be instituted as soon as the infant is born.

Full protection might be afforded high risk infants, the researchers concluded, by combining HBIG injection at birth with follow-up administration of a promising hepatitis B vaccine still being tested. Vaccines do not become effective immediately. The HBIG would provide temporary protection against infection until the infant developed active immunity to the vaccine.

The study was a collaborative effort of Wolf Szmuness, M.D., of the New York Blood Center, and R. Palmer Beasley, M.D., of the University of Washington Medical Research Unit in Taipei, Taiwan. The infants were treated under the direction of Dr. Beasley at the Maternity and Child Health Center of Taiwan Provincial Junior College of Nursing. ■

Researchers Note Cellular Responses May Help Heal Wounds and Unclog Blocked Arteries

By Hilah Thomas

Investigators at the National Institute of Dental Research (NIDR) report that similar cellular responses may initiate wound healing and hardening of the arteries.

In response to trauma, platelets—small cell-like particles in the blood—are known to bind to the injured tissue and release several substances. One of these substances, the platelet-derived growth factor, causes certain cells to divide. The NIDR team has found that this growth factor also stimulates the directed migration of fibroblasts and smooth muscle cells—which are involved in tissue repair.

The ability of a chemical to attract cells is known as chemotaxis. It is studied by measuring the migration of cells across a porous membrane separating two chambers. Cells are placed in the top chamber and the attracting substance to be tested is put in the bottom. With small amounts of platelet-derived growth factor in the lower chamber, muscle cells and fibroblasts are attracted to crawl through the filter to the bottom chamber. Other growth factors including insulin, epidermal growth factor, fibroblast growth factor, and nerve growth factor have no chemotactic activity on these cells even at high concentrations.

Scientists now think that in a wound, fibroblasts are attracted into the damaged area by platelet-derived growth factor and then stimulated to multiply, thus rebuilding the tissue. Similar events could also occur in the formation of atherosclerotic plaques in blood vessels. Damage to endothelial cells exposes a surface to which platelets first bind, subsequently releasing the platelet-derived growth factor. This hormone-like wound factor can attract smooth muscle cells from the center of the blood vessel wall to its inner surface. There they multiply, deposit matrix material and form a scar to temporarily repair the damage. However, under conditions of dietary excess, the plaque can become permanent. Numerous patches of plaque reduce a vessel's flexibility, hinder blood flow and interfere with normal functioning.

Drs. G.R. Grotendorst, H. Seppa, H.K. Kleinman, and G.R. Martin reported these findings in the *Proceedings of the National Academy of Sciences, USA*, in June 1981. ■

DES, a Cancer-Causing Agent in Women, Becomes an Important Tool in Research

By Thomas Hawkins

Diethylstilbestrol—DES—the substance that was found to cause a rare vaginal cancer in young women whose mothers were treated with the drug during pregnancy has proven to be an effective research tool. Researchers are currently investigating the ways in which environmental agents suppress the body's immune systems. The work is being done at the laboratories of the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina.

The investigators found that DES-treated animals had a lowered number of lymphoid cells in the thymus and bone marrow, key sites in production and activity of these cells. They also saw a marked decrease in the animal's ability to ward off parasites, tumor cells, bacteria and toxins.

For example...DES-treated animals eliminated *Trichinella* worms less readily than control animals...were more likely to develop tumors after tumor cell injection than were controls...were less able to summon biological defenses against bacteria and bacterial toxins.

Immunology is an emerging field in environmental health sciences. Investigators have begun to look at the ways in which environmental agents may affect the immune systems. Suppression of the immune system may represent an important target organ toxicity and may explain many yet undefined environmental toxicities.

DES is of special interest because of its connection with vaginal cancer in young women, its apparent relation to genital malformation and dysfunction among male offspring of treated mothers, and breast enlargement and low sperm counts among occupationally exposed males. It has also been widely employed to increase weight in cattle and other livestock. It is one of a number of synthetic compounds present in the environment found to have estrogenic activity.

The NIEHS/NTP researchers, including Jack H. Dean, Ph.D., Michael Luster, Ph.D. and Gary A. Boorman, Ph.D., have recently published three papers outlining their work with DES in the *Journal of the Reticuloendothelial Society*. The word reticuloendothelial refers to the system of cells in the body that provides defenses against biological and chemical attacks. The defense usually takes place when one of the specialized cells ingests the invading organism or particle and breaks it down into substances that can be cleared from the body. A second defense mechanism encloses the invader so it cannot interfere with the normal processes of the host animal.

"Our work doesn't establish a cause and effect relationship between DES-related cancer and these various alterations of the immune response," Dr. Dean said. "However, we've demonstrated that exposure to chemicals such as DES ca produce immune alterations and result host resistance changes. Thus the immune system appears to be a sensitive target organ for defining cellular toxicity."

This work is being done by the Immunological Toxicology Program, which is a cooperative effort between the Laboratory of Environmental Chemistry at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina, and the National Toxicology Program, of which NIEHS is one member component. ■

The NIEHS/NTP researchers, left to right, Michael Luster, Ph.D.; Gary A. Boorman, Ph.D.; and Jack H. Dean, Ph.D. published recent work on the use of DES as a research tool in investigating the ways in which environmental agents suppress the body's immune systems.

NIH PHOTO #1712

No Direct Cause and Effect Found Between Low Blood Cholesterol and Cancer

Prepared by the National Institute of Dental Research

Reducing elevated cholesterol by diet or other means is still considered to be beneficial according to data presented recently at a Workshop on Cholesterol and Non-Cardiovascular Mortality.

The workshop, sponsored by NIH's National Heart, Lung and Blood Institute and the National Cancer Institute, was a follow-up to an earlier meeting held in 1980, at which eight epidemiologic studies were reviewed to examine a possible relationship between low serum cholesterol and increased risk of cancer. At that time, the data from three of the studies presented (Framingham, Puerto Rico and Honolulu) suggested such a relationship, but the others did not. The panel from that workshop recommended another panel be convened when additional data from these and other studies might be available.

From the 17 studies reported in the current workshop, an inconsistent relationship between cholesterol concentration and death from cancer was found. For instance, in addition to Framingham and Honolulu, six other studies found an inverse association between serum cholesterol and death due to cancer in men. However, none of the studies found significant association in women.

Furthermore, in four studies (Framingham, Hawaii, Stockholm, and Hiroshima-Nagasaki) a significant association between low blood cholesterol and colon cancer in men was found. No other specific sites of cancer showed a significant association in more than one study. In the studies that suggested it, the excess cancer risk tended to be most pronounced at the lowest end of the cholesterol distribution for that population.

If the increase in risk of colon cancer is real (and this is still uncertain), the question arises as to what if anything is responsible for the increase.

Among the factors mentioned at the 1980 meeting and repeated at this one, is that the correlations observed may reflect traits, possibly genetic, present in only small numbers of individuals or may reflect long-standing pre-cancerous disease. The data reviewed at the workshop suggested a number of avenues of research of potential usefulness in clarifying any association between serum cholesterol level and cancer risk.

Among the research topics suggested were: studies on bile acids and dietary lipids in relation to the absorption of dietary Vitamin A, a substance that appears to confer some degree of protection against tumors; studies on whether depletion of cell membrane cholesterol when serum cholesterol levels are unusually low might be a factor in pre-cancerous cell changes or tumor induction; continued research on genetic determinants of cholesterol metabolism, plasma cholesterol levels and bile acid turnover, especially in persons with very low cholesterol levels.

In summary, the panel of experts concluded that although there is inconsistent but confirming evidence of a possible increased cancer risk at very low cholesterol levels in men, the magnitude of the risk, when present, is generally modest.

In addition, no basis was found to recommend changing the widely held position that elevated blood cholesterol poses a definite risk from premature arteriosclerosis and its complications. There was unanimous opinion that the data did not contradict the current public health message that individuals with elevated cholesterol levels should have such levels reduced through diets lower in saturated fat and cholesterol. ■

Walnut Creek Study of the Pill Receives Mixed Reviews

By Maureen Gardner

Health risks to young, healthy nonsmoking women using oral contraceptives appear to be lower than previously thought, according to the final report of the Walnut Creek Contraceptive Drug Study. Cautions are still warranted for many women, however.

"Oral contraceptives harbor measurable risks for certain women and their use should be carefully weighed by a woman and her physician," according to Dr. Philip Corfman, Director of NICHD's Center for Population Research, which supported the study. Walnut Creek and other studies show that oral contraceptive users who smoke or who are over the age of 30 have increased risks of developing serious side effects, particularly circulatory disorders.

Between 1969 and 1977, the Walnut Creek study followed more than 16,000 women to compare rates of disease and death among current Pill users, past users, and those who never used the Pill. The women in the study, members of a comprehensive health care program at Kaiser-Permanente Medical Center in Walnut Creek, California, were between the ages of 18 and 54, and the majority were white, middle class, and healthy.

Results of the study indicated that oral contraceptive users do not have an increased risk of death compared with non-users. In addition, results showed that use of the Pill apparently does not lead to breast cancer or benign ovarian tumors, and may even offer protection from fibrocystic breast disease and cancer of the endometrium. Researchers also noted that the risk of high blood pressure seems to be lower than previously reported.

Some health risks were detected, however. Walnut Creek results confirm that the negative effects of smoking are intensified in women who use the Pill. Heavy smokers in general have an increased risk of developing heart disease and other circulatory disorders, but those who also take the Pill are even more vulnerable. According to Walnut Creek researchers, "smoking should be considered a contraindication to oral contraceptive use, or at the very least, women wishing to use oral contraceptives should be strongly urged not to smoke."

Walnut Creek results show that certain lifestyle factors may predispose women to some health problems associated with oral contraceptives. For instance, the results reaffirm that women who are more sexually active, as were those on the Pill in this study, are more likely to develop lower urinary tract infections and cancer of the cervix. Because of this known association, the Pill's possible role in these disorders could not be isolated in this study.

A new finding emerging from the Walnut Creek study is the apparent increased risk of malignant melanoma, a form of skin cancer, in oral contraceptive users. However, the Pill users in the study sunbathed more often, and from the data available it was not possible to separate the effects of the Pill from exposure to the sun's cancer-causing untraviolet rays. The NICHD is supporting further research on the tentative relationship between oral contraceptives and malignant melanoma.

Although the study was not primarily designed to monitor relatively uncommon events, states Dr. Corfman, apparent links between oral contraceptives and certain kinds of stroke and blood clots were found. Overall, he emphasizes that the findings of the study "cannot be considered final, and must be weighed with evidence from other clinical and epidemiological studies." ■

Rocky Mountain Spotted Fever: A Dramatic Rise in Cases

By Susan Gerhold

One type of tick that carries Rocky Mountain Spotted Fever is shown at left. The male of the species is on the left. NIH PHOTO #1713

Magnified tick eggs are shown here in the process of hatching. NIH PHOTO #1714

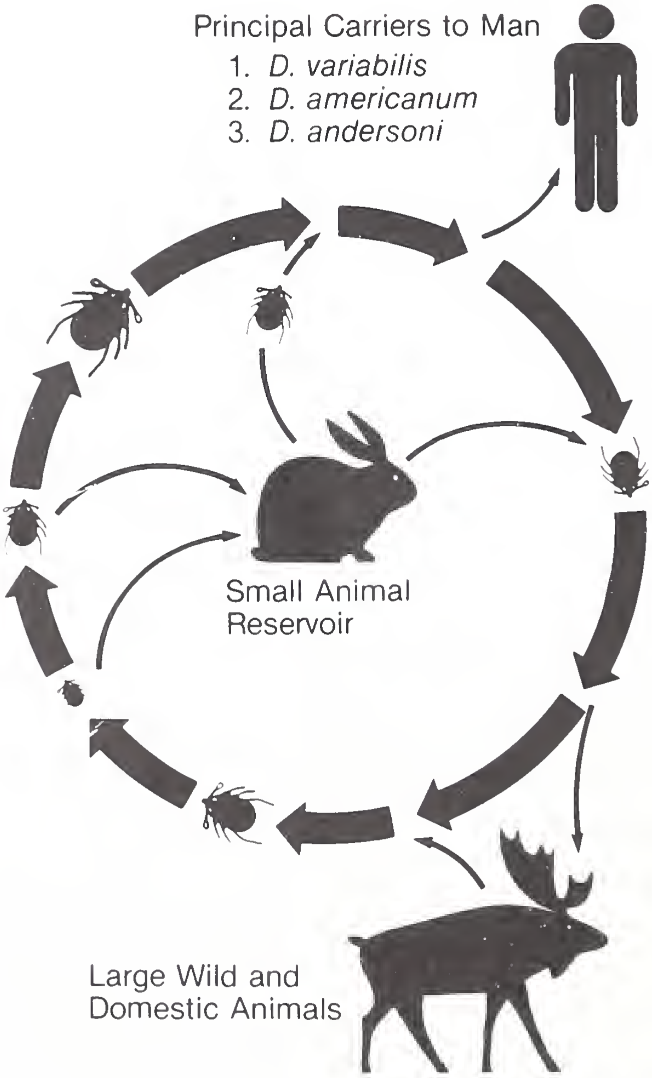
Photos compliments of the National Institute of Allergy and Infectious Diseases (NIAID).

Last year the Centers for Disease Control (CDC) reported more than 1,000 cases of Rocky Mountain Spotted Fever, a disease caused by a group of organisms called *Rickettsia rickettsii* and transmitted by ticks. This disease, first discovered over 100 years ago in Montana, Utah, and Colorado, has in the past few decades been more common in the Southeastern states of Maryland, Virginia, Tennessee, South and North Carolina, Oklahoma, and Georgia than in the Rocky Mountain area. Reported cases this year exceed last year's number, and NIAID researcher Robert Philip's prediction of a record-breaking year may be accurate. Nearly 500 cases were reported as of July; 90 percent of these cases were concentrated in the Southeastern United States.

The U.S. Public Health Service has studied the disease since 1902 in the Bitterroot Valley of Montana. The causative organism, *Rickettsia rickettsiae*, is named after Howard Taylor Ricketts, who studied the disease in the Bitterroot area from 1906 to 1909. He identified the wood tick, a tiny insect with many legs, which was responsible for transmitting this disease. Because Rocky Mountain Spotted Fever was so prevalent in the Bitterroot Valley, the U.S. Public Health Service established a resident field station in 1921 in Hamilton, which later evolved into the Rocky Mountain Laboratory of NIH's National Institute of Allergy and Infectious Diseases (NIAID).

Later, Dr. R.A. Cooley, a Montana entomologist, surveyed the state and studied the life cycle of the wood tick. He found that the adult tick feeds on large animals such as horses, cows, and goats for nine days and then the female tick drops to the ground to lay thousands of eggs. The female then dies and the eggs hatch within a month. The baby ticks grow into 6-legged larvae or seed ticks, living on rodents for several days. Developing another pair of legs, the tick then enters the nymph stage, feeding on small animals for several days, and then drops to mature into an adult tick.

Researchers have found that the entire life cycle of the tick is two years and that an infected tick transmits disease only during its feeding time and only when it reaches maturity. The disease, however, is transmitted and retained stage by stage in the tick's life with the female tick passing on the organisms to her eggs.



The cycle by which Rocky Mountain Spotted Fever is diagramed above. Animals bitten by infected ticks serve as living reservoirs of the disease and as a source of infection for more ticks. The disease is spread to man when he is bitten by the infected tick. NIH PHOTO #1715

NIAID researchers also know that rickettsia are structurally related to bacteria and cause an illness that resembles a viral infection. After a tick bite, the victim experiences chills, high fever, headache, and bone pain. A rash may also appear on the wrists and ankles, one of the main clues used by physicians to diagnose spotted fever.

In severe untreated cases, the fever may continue and pulmonary and circulatory complications may occur. Full recovery sometimes takes several weeks or months if the victim is not treated immediately.

Dr. Philip and his staff at the NIAID Rocky Mountain Laboratory are currently focusing their research on determining why certain areas or "pockets" report cases of spotted fever, and other parts of the same state do not report any cases at all. He also said they are working with other rickettsial organisms found in the tick that do not cause disease to see if these organisms interfere with Rocky Mountain Spotted Fever and produce some type of immunity.

Dr. James Williams, also of the Rocky Mountain Laboratory, is working with University of North Carolina physician David Walker in studying and identifying the antigens that specifically relate to infection. From these studies the researchers can determine which antigens should be present in a future vaccine to fight the spotted fever.

NIAID contractors Dr. Catherine Wilfert of Duke University, and Ernie Austin and Vivian Dickinson of the North Carolina Health Department, are currently working together on an intense epidemiologic study focusing on antibodies and how effective they are in preventing spotted fever in North Carolina counties that have the highest incidence of tick bites in the country.

Under a contract from NIAID, epidemiologists at Maryland University, Johns Hopkins, and the Maryland State Health Department, are studying whether the population movement from urban areas to surburban areas may be causing an increase in tick bites in the Mid Atlantic states.

A Rocky Mountain Spotted Fever vaccine had been on the market for a number of years; however, it was determined to be ineffective and is no longer commercially available. A new vaccine developed at the U.S. Army Research Institute for Infectious Diseases, Fort Detrick, Maryland, was shown, in animal studies, to be superior to the older vaccine. It was also shown, in collaboration with the NIAID, to be safe in human volunteers. An efficacy study in humans has recently been completed at the Center for Vaccine Development, University of Maryland, Baltimore. Although the data from this study are not yet completely analyzed, it appears that the new vaccine also may not be very effective in preventing Rocky Mountain Spotted Fever. Although it is possible that this vaccine may be improved, the most promise for a future vaccine apparently lies with studies which are still in the laboratory stage.

For more information on Rocky Mountain Spotted Fever, contact the National Institute of Allergy and Infectious Diseases, Office of Research Reporting and Public Response, Building 31, Room 7A32, NIH, 9000 Rockville Pike, Bethesda, Maryland 20205. ■

Primates with Vitamin Deficient Diets Prone to Gum Disease

By Maureen Mylander

Recent studies supported by the National Institute of Dental Research now offer the first concrete evidence that a diet deficient in Vitamin C significantly increases susceptibility to periodontal or gum disease.

This report by Olav Alvares and colleagues at the University of Washington concludes that periodontal tissues of animals fed a diet marginally deficient in Vitamin C (ascorbic acid) are more susceptible to breakdown when challenged by experimentally-induced dental plaque, a deposit of material on the surface of the teeth.

Periodontal (gum) disease, a leading cause of tooth loss among adults after age 35, has long been thought to result primarily from the body's long-term reactions to certain bacteria and their products. However, scientists have long suspected that nutrition may also influence the maintenance and breakdown of periodontal tissues. For example, there is strong evidence already that Vitamin C is necessary for adequate repair.

Periodontal disease has long been associated with acute Vitamin C deficiency as in Scurvy. Vitamin C deprivation in industrialized societies has seldom been severe enough to be clinically evident.

The investigators induced gum disease in two groups of monkeys by tying a silk thread around a single molar tooth at the gum line. In two weeks, the marginally deficient animals showed 36 percent greater inflammation in the gum tissues and a 41 percent greater periodontal pocket depth around the encircled teeth than a group of control animals given the same amount of food but with adequate Vitamin C.

The study also revealed clues which may account for this breakdown. The protective functions of polymorphonuclear leukocytes (PMNs)—white blood cells normally rich in Vitamin C—were compared in both groups of animals at various points throughout the experiment. At the start of the experiment, PMN ability to engulf *Candida albicans*, a test organism, was equal in all the animals.

However, at 23 weeks (namely at the time of the experimentally-induced periodontitis), PMN's of the marginally deficient animals showed a significant reduction in chemotaxis (the migration of leukocytes to antigen-containing sites) and in phagocytosis (the ability to engulf microorganisms) compared to PMN function in the controls.

Another recent report by Olav Alvares and Ivens Siegel (*J. Oral Pathology*, 1981; 10: 40-48) identifies a second factor that is altered by a diet deficient in Vitamin C. Monkeys fed diets with no Vitamin C experienced an increase in the permeability of the inside lining of the gum that could have contributed to the development of spontaneous inflammation. Other investigators have reported that oral ascorbic acid supplementation led to a decrease in permeability of the same tissues.

In healthy individuals, the gum's outer tissue ordinarily impedes or minimizes the passage of antigenic and toxic substances from the surface into the underlying connective tissues. But when the permeability of this surface increases, the noxious substances from bacteria can enter the periodontal tissues more easily and damage them.

The findings described here, together with previously established evidence, indicate several mechanisms by which Vitamin C may aid the body in defending itself against periodontal disease.

This report will be published in the *Journal of Periodontal Research.* ■

Leading Clues to Brain Disorders Take Scientists All Over the World

By Ray Fleming

Their research spans half a world, from the rolling countryside of Maryland to the tropical island of Guam, and hundreds of years, back to the primitive jungles of New Guinea.

They go where they think the answers are. And the victims of amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, and a host of other neurological disorders may someday benefit from their discoveries.

They are the scientists of the Laboratory for Central Nervous System Studies, a part of the National Institute of Neurological and Communicative Disorders and Stroke. Their approaches to neurological problems are as different as the locations in which they find their data, but their goals are the same: to conquer the baffling brain disorders that continue to devastate patients and their families.

Dr. Clarence J. Gibbs, Jr., a microbiologist and deputy chief of the Laboratory, has worked for many years with so-called "slow" viruses: viruses that lie innocently in the body for long periods until they suddenly become active and dangerous. He and his fellow investigators at their Ft. Detrick, Maryland, laboratory are now involved in a long-range program to link viruses of this and other types to brain disorders. The research team is attempting to transmit over 50 disorders, including epilepsy, amyotrophic lateral sclerosis, and Alzheimer's, Huntington's, and Parkinson's diseases, to laboratory animals by inoculating them with diseased tissue.

Dr. Gibbs suspects that some of these human disorders may be caused by hidden viruses that are "triggered" to become active by some genetic switch. "It's also possible," says Dr. Gibb, "that people who develop these diseases are missing some factor that allows the body to fight off a destructive virus. By studying the inoculated animals that develop disease, we hope to define the nature of the responsible virus or viruses that we have isolated and discover an immune or genetic factor that makes them destructive."

Dr. Gibbs cautions that the development of symptoms in animals, which would indicate successful transmission of disease from human tissue, may not be apparent for many years, as is the case in many neurological disorders. But he is confident that, having already transmitted two such diseases (Kuru and Creutzfeldt-Jakob disease) successfully, he can learn how other disorders develop.

In contrast to the broad, basic approach to neurological disorders followed by Dr. Gibbs, other scientists at the Laboratory for Central Nervous System Studies are linking specific research findings with individual disease. In the case of amyotrophic lateral sclerosis (ALS), for example, Laboratory investigators are taking a hard look at the amounts of certain metals present both in patients and in their environments.

For years, Japanese scientists have observed unusual mineral compositions in the drinking water and garden soil of areas in Japan and Guam where high numbers of ALS victims live. Low amounts of environmental calcium and magnesium, and high amounts of aluminum and maganese, were also noted. Investigators from the Laboratory, collaborating with Japanese workers, have now discovered low calcium and magnesium levels and high aluminum and iron levels in water and soil samples from southwestern New Guinea, where ALS incidence is also high.

The possible significance of this promising clue has not been lost on the Laboratory's scientists, who have now launched an expanded study of metal levels in the environment and tissues of ALS patients. The investigators hope the project will define the role metals play, if any, in the development of the disease.

Neuroscientists at the Laboratory suspect that what they learn from the environmental clues they uncover may be doubly important in light of the re[illegible] past. That ALS might be partly the result of an environmental factor, for example, was first suggested when Laboratory studies showed high incidence of the disorder in Japan, Guam, and Western New Guinea. But information compiled by the Laboratory now shows that over the past 20 years the number of ALS victims has gradually decreased in Guam and Japan, while the disorder is on the rise in New Guinea. One Laboratory scientist speculates that gradual modernization in certain areas of Guam and Japan and a rising standard of living may be eliminating any environmental factors at work in the disorder there. Western New Guinea, on the other hand, remains an area of primitive conditions where such a factor may still be thriving. Identifying the reason for the change in ALS incidence would help bring investigators a step closer to eventually solving the mystery of a devastating neurological disorder.

Developing animal models, analyzing metal levels, studying diseased populations: each is a different approach to the problem of brain disorders. But for the scientists at the Laboratory for Central Nervous System Studies, each is an approach that holds much promise for patients and their families. ■

Surgery or not? Especially When it Comes to Dental Disease—What are the Alternatives?

A workshop on surgical therapy for periodontitis, a chronic inflammation of the gums that causes tooth loss in millions of Americans and surpasses even dental caries as an oral health problem, was recently sponsored by the National Institute of Dental Research (NIDR).

The meeting opened with discussion of a background paper reviewing the existing literature, followed by several state-of-the-art papers by distinguished researchers and academicians. From this body of information, plus critiques and comments from the audience, a review panel made recommendations in five areas: when is periodontal surgery necessary? what are its risks? are there feasible alternatives to surgical treatment? what are the risks in delaying surgery? and what are the research needs?

The panel's preliminary report concluded that where root surfaces are accessible to instrumentation and plaque control is thorough, either by patients or professionals, active disease can be arrested. Where root surfaces are not accessible, periodontal surgery is an appropriate form of therapy to gain access for root preparation, and for removal of local irritants that are difficult to reach. It was also found that when surgery is combined with meticulous plaque control, it is effective in stopping loss of attachment of soft tissues to the teeth, and may thus provide a means of controlling disease when nonsurgical methods are ineffective.

Some of the discussion on alternatives to surgery concerned a recent therapy that uses root planing and subgingival scaling—the removal of bacterial deposits from tooth surfaces—plus the home use of salt solutions, oral irrigating devices and oxidative mouthwashes. The panel noted that claims of the effectiveness of this technique have not been substantiated in controlled studies. The workshop attendees were advised that th[illegible] NIDR has issued a Request for Propo[illegible] and that in the near future a contract will be awarded for a controlled clinical study in this area of research. ■

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

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National Institutes of Health
Building 31, Rm. 2B-10
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October 1981

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Immediate Treatment to Comatose Patients Reduces Mortality Rate **p. 11**

Scientists Identify Proteins to Help Diagnose Neurological Disorders **p. 11**

Replacing Enzymes May be the Key to Treating Lipid Storage Diseases **p. 4**

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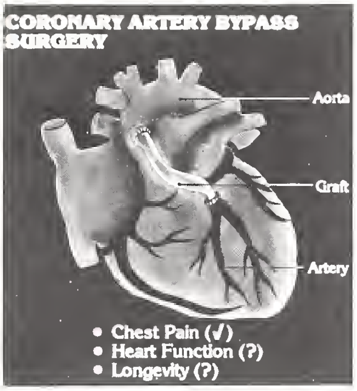
News&Features
from NIH

October 1981

Neurological disorders such as Gaucher's, Tay-Sachs, and Fabry's diseases all have one thing in common—their victims suffer from a dangerous buildup of fatty substances in their bodies. Patients seen at the NIH research hospital suffer from swollen organs, damaged and lost nerve cells, bone degeneration, and reduced white cells and platelets.

NINCDS researchers have found that the cause of the trouble is a shortage of enzymes—proteins that breakup the fatty lipids. Researchers are currently trying to replace the enzyme and direct it to the site where excessive amounts of lipids are stored. This replacement therapy in preliminary clinical trials has lowered the lipid level in the blood and liver of some patients and [illegible]roved their health. See page 11



According to cardiology specialists and researchers attending an NIH Consensus Meeting held several months ago, coronary artery bypass surgery improves the life expectancy of patients suffering from a narrowing of the left main artery and those patients suffering from heart disease affecting all three major coronary vessels.

However, the conference participants were unable to agree on whether the role of coronary artery bypass surgery on patients with other heart disease problems would be helpful. See page 3

Under an NICHD grant, researchers at Boston University studied more than 500 women between the ages of 25 and 49 and who had suffered their first heart attack. They compared the medical history and drug use of these women with more than 2,000 age-matched controls.

Results showed that women who used oral contraceptives for five years or longer seem to be at greater risk for heart attacks and they continue to be in the high risk category at least 9 years after discontinuing the pill. See page 10

Kidneys donated from living relatives seem to function more effectively and for a longer period of time than those kidneys that come from cadavers.

NIAID researchers studied the differences between transplanting living kidneys to patients versus kidneys that are donated by people, who after they die, allow their organs to be used for transplantations. See page 9

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First Symposium Held on Tourette Syndrome: Dr. Samuel Johnson's Case Discussed

By Ray Fleming

"You must not mind me, madam; I say strange things but I mean no harm."

The year was 1778, and the man behind these words was a now-famous Englishman; a critic and author alternately considered a genius and an idiot by the people of his time. He was a frequent contributor to literary magazines, yet he talked to himself, grunted, and repeated incoherent words and phrases.

He published a dictionary, and started a club of well-known literary figures. But he rocked back and forth on his feet, rolled his head, and couldn't approach a doorway without measuring his steps exactly.

Dr. Samuel Johnson, the "great prince" of literature, suffered from Tourette syndrome.

Were Dr. Johnson alive today, his illness would be more easily recognized for what it actually is: an organic disorder of the central nervous system. Although treatment of TS has improved considerably with the advent of drugs like haloperidol and clonidine, public awareness of the condition is still developing.

Thousands of Tourette patients continue to suffer physically and mentally from the strange behavior, sudden body movements, and involuntary sounds that characterize the disorder. The cause of the illness has yet to be discovered.

The movement and behavior patterns of TS patients were discussed at great length recently in New York City at the First International Symposium on Tourette Syndrome and Related Disorders. A cosponsor of the symposium was the National Institute of Neurological and Communicative Disorders and Stroke.

Symposium speakers emphasized that unlike the simple, well-defined body movements occurring in disorders like Parkinson's and Huntington's diseases, TS movements are often complex ones requiring coordination.

Spasmodic "tics" are common in the head and neck, and occasional in the arms, hands, and legs. Compulsive behavior, such as lip smacking, grimacing, sniffing, saluting, and jumping also occurs frequently.

Motor tics, which occur more often in male than in female TS patients, were discussed in detail. TS movements are involuntary and can occur in a sequence according to a pattern; the tics also happen suddenly and at irregular intervals, rather than continuously.

Such tics vary in frequency (temporary remissions are common), in severity, and in location in the body. Unlike the spasms produced by some other movement disorders, TS tics do not generally result from sensory stimulation.

Many patients, it was reported, feel an irresistible urge to perform an abnormal movement, and are relieved when the tic is completed. (Some TS sufferers are temporarily able to suppress tics, but the urge must be satisfied within a short period of time.)

Many feel inhibited by their tics: one young patient, for example, balked at showering because he felt that once he began the process, he would not stop. The reason for these seemingly contradictory symptoms according to some scientists, may lie in the dual inhibiting/activating nature of the brain's chemical messenger system.

"We suspect that the movement and behavior problems in Tourette syndrome are caused by a chemical abnormality in the brain's neurotransmitter system," explained Dr. Thomas Chase, NINCDS scientific director and cochairman of the symposium. "The resulting symptoms vary considerably from patient to patient."

One symposium presenter chose the case of Dr. Johnson to illustrate the variety of TS symptoms. The English lexicographer repeatedly tilted his head toward his right shoulder while talking or sitting, and would compulsively touch his toes or heels together as if to form a triangle.

One of his best-known compulsions was deliberately touching every post he passed as he walked along the street. He also habitually kept his left arm fixed across his chest, with his hand resting under his chin.

Dr. Johnson suffered another symptom characteristic of TS: compulsive uttering of barks, grunts, and other noises, sounds and words. Such utterances plague TS patients to this day, and in the most distressing form manifest as coprolalia, the irresistable urge to utter obscenities.

Although Dr. Johnson himself did not curse, compulsively, 50 percent of TS sufferers do. Some scientists claim that this symptom has psychological origins, since it seems unlikely that a physical disturbance would encourage the use of obscene words over thousands of socially acceptable ones. Other investigators claim an organic basis for coprolalia.

Using tables that reflected how often letters and letter combinations appeared in normal language, scientists programmed computers to generate strings of random letters, each letter weighed with its probability of occurrence in normal speech.

Some of the first recognizable letter combinations produced by the computers were common obscenities. Religious profanities were not produced in computer-generated language—just as they are not found in coprolalia.

Since a number of TS patients claim that the sound of words is the most important factor in satisfying their urge to vocalize, the investigator argued that TS patients who "curse" do so because obscenities are among the first, simplest, and most satisfying words produced by a short-circuited nervous system. Religious profanities, he suggested, are absent because they may be more difficult to produce and less satisfying to the patient.

Samuel Johnson, a noted literary genius of his time (1709-1784) suffered from Tourette syndrome (Photo courtesy of the National Library of Medicine.) **NIH PHOTO 1717**

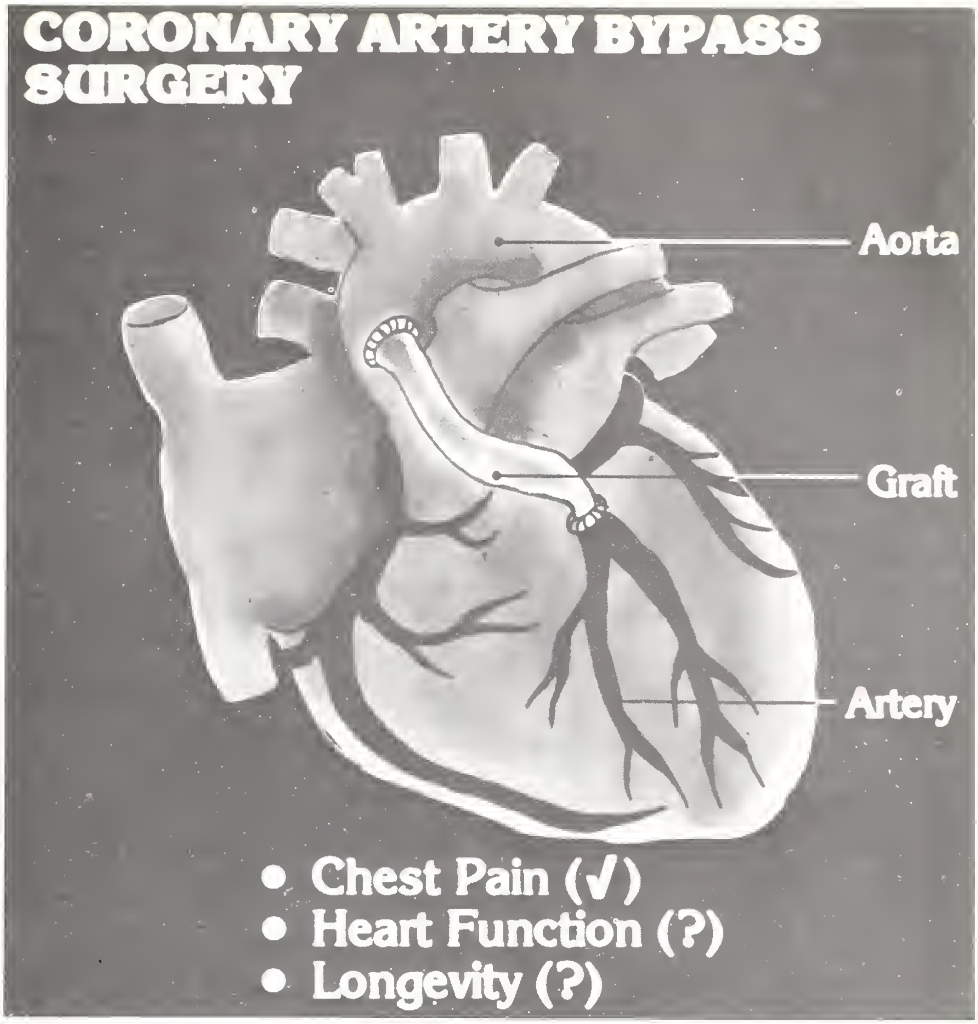
The basis of coprolalia is still open to question. Through the research supported by NINCDS, the Tourette Syndrome Association, and other agencies, more pieces of the Tourette puzzle may fall into place.

Animal model and clinical studies of TS and TS-like disorders continue to provide information, and promising drugs are being tested for better control over symptoms. Recent media publicity has resulted in increased public awareness about the disorder and its distressing characteristics.

"Tourette syndrome has been plagued by too much clinical misunderstanding and too little research attention," concluded Dr. Chase. "We hope we can now better define what the syndrome really is and apply emerging techniques to the solution of the problem." ■

Consensus Development Conference Finds Coronary Artery Bypass Surgery Helpful

By Bill Sanders



Coronary artery bypass surgery helps alleviate chest pain and often improves the patients' life style. However, questions arise on whether this procedure is effective and useful for all types of heart disease patients and if the technique provides a longer life for those suffering from heart disease. **NIH PHOTO 1718**

A Consensus-Development Conference on coronary artery bypass surgery, held at NIH several months ago, concluded that this surgical procedure represents a major advance in the treatment of certain subsets of patients with coronary heart disease.

Available evidence indicates that, compared with conventional medical management, the operation improves life expectancy among patients with critical stenosis (greater than 50 percent narrowing) of the left main coronary artery, which provides most of the blood supply of the left ventricle; and surgery probably improves longevity among patients with significant disease affecting all three major coronary vessels.

The operation usually provides relief of symptoms in 80-90 percent of patients with stable angina; and in patients with unstable or crescendo angina, surgery is indicated if symptoms are not relieved by intensive medical therapy or if the condition is recurrent.

Surgery may better the quality of life in other properly selected patients by improving cardiac perfusion and performance, reducing the frequency of cardiac-related events, or reducing the amount of medication needed to control symptoms. Patients who do not respond well to medical management or whose lifestyles are adversely affected thereby may also stand to benefit from surgery. This decision should therefore be made by the physician and his patient after a reasonable trial of medical therapy, with periodic re-evaluation of the patient's response.

The conference participants reached no consensus on the role of coronary artery bypass surgery in the management of patients with atypical angina, in which coronary spasm may be a major component; patients with severely impaired ventricular function due to ischemia; or patients experiencing acute heart attacks, intractable arrhythmias, or myocardial blood deprivation in the absence of symptoms. In patients with one and two-vessel disease (except the left main coronary artery) the participants felt that the decision concerning whether or not to resort to surgery was best left to the physician and his patient; but all agreed that medical management, not surgery, was indicated for the patient with symptoms but no critical stenosis of any coronary branch.

Currently, more than 100,000 coronary artery bypass procedures are done each year in the U.S. Operative mortality and complications such as perioperative heart attacks have declined steadily with improvements in operative technique, anesthesiology, and methods for protecting the heart during the operation. At the most experienced centers, operative mortality rates below 2 percent are usual and the conference participants feel that, among patients with stable angina and good ventricular function, mortality rates below 4 percent are achievable at most hospitals. Among patients with unstable angina, the operative risk is somewhat higher and among patients with severe ventricular impairment it is higher still; however, the procedure provides striking symptomatic relief in most patients and also promises a longer and more enjoyable life to many victims of coronary heart disease. ■

Enzyme May be Useful in Screening for Post–Transfusion Hepatitis

By Bronna Cohen

Two recent studies funded by the National Institutes of Health have verified an association between elevated donor blood levels of an enzyme called alanine aminotransferase (ALT) and incidence of post-transfusion hepatitis (PTH) in recipients of that blood. These results suggest that prescreening of donor blood for ALT levels might significantly prevent PTH, though at the cost of donor units.

Hepatitis following transfusion of blood and blood products has been a problem since the technology of transfusion was first developed forty years ago. Constant efforts since then have resulted in progress against post-transfusion hepatitis, but have not eradicated the problem.

Three different types of hepatitis have been recognized: type A, type B, and a third type that has been named non-A, non-B (NANB) hepatitis. Hepatitis A and B are known to be caused by viruses, and each can be detected by simple serological tests. Almost all cases of post-transfusion hepatitis not identified serologically as type A or type B are classified as non-A, non-B hepatitis. A causative agent for this illness has not been found nor has a serological test for detecting it, despite much scientific effort.

Hepatitis type A, previously known as "infectious hepatitis," is usually an epidemic, community-acquired disease transmitted by the fecal-oral route. Generally, hepatitis A is not associated with post-transfusion hepatitis. Hepatitis type B, previously referred to as "serum hepatitis," is commonly associated with parenteral drug abuse and transfusion of blood and blood products. However, because of routine serological screening of all donor blood prior to transfusion, hepatitis B has virtually disappeared as a serious complication of blood transfusion.

Nevertheless, the spread of hepatitis through blood transfusion is still a widespread public health problem in the U.S. Current estimates are that every year 100,000 to 150,000 people contact detectable post-transfusion hepatitis. About 90% of this hepatitis is non-A and non-B. Investigators have concentrated on finding the agent, or agents, that cause non-A, non-B hepatitis, and on the development of reliable laboratory test to detect it. Neither effort has been clearly successful.

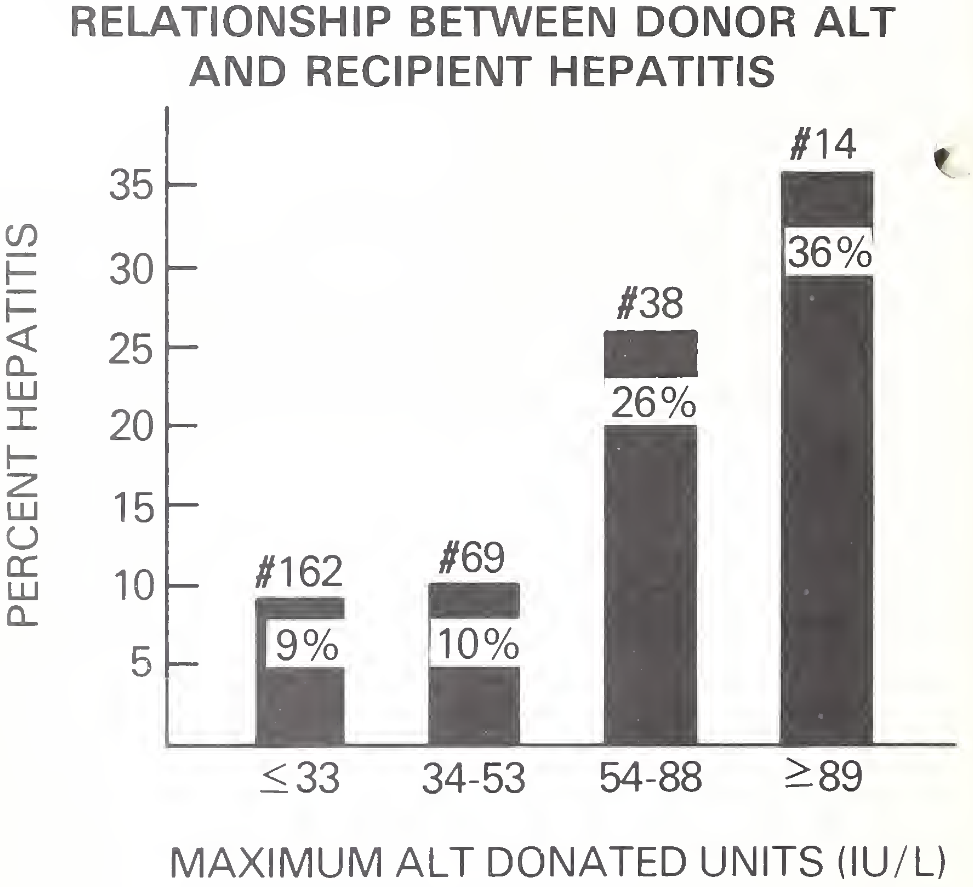
In the absence of a direct method for detecting non-A, non-B hepatitis in blood, scientists have begun investigating indirect testing methods. One such indirect assay, the ALT assay, uses the blood level of ALT, an enzyme manufactured in the liver, as an indicator of the presence of hepatitis. It was theorized that patients infected with hepatitis might have some degree of liver damage, and, therefore, might have elevated concentrations of liver enzymes such as ALT in their bloodstreams.

The Transfusion-Transmitted Virus (TTV) Study funded by the National Heart, Lung, and Blood Institute was the first large-scale study to apply the ALT test to donor blood and then monitor the incidence of PTH among patients transfused with that blood. The TTV study involved 1,513 patients and took place in several centers across the U.S. over a period of six years. Results of the research were released in 1981, and showed a significant association between donor blood ALT levels and recipient non-A, non-B hepatitis. The study group suggested that up to 40% of cases of post-transfusion hepatitis would be prevented by rejecting all blood with a blood ALT level greater than 45 international units (IU).

Scientists working at the NIH Blood Bank and the National Institute of Allergy and Infectious Diseases conducted a clinical trial that further explored the association of donor ALT level with recipient hepatitis. The NIH researchers found that among 283 patients who received blood transfusions after undergoing open heart surgery, 12.7% developed hepatitis, of which 97 percent was NANB. The ALT tests on 3,359 donors to these patients indicated that the risk of hepatitis was significantly associated with the level of donor ALT.

Twenty nine percent of 52 patients receiving at least 1 unit of blood with the ALT level greater than 53 IU had hepatitis develop, compared with 9 percent among 231 recipients who were given only blood with an ALT level of 53 IU or less. These results suggested that ALT testing of donors could prevent 29 percent of PTH at the loss of 1.6 percent of donor units.

Although these results are encouraging, important questions remain unanswered by the results of the two studies. First, the ALT test cannot be used to exclude every infectious blood unit. In the TTV Study, 7 percent of patients who received multiple blood transfusions acquired non-A, non-B post-transfusion



Estimates state that over 100,000 people every year contract hepatitis. This chart shows the relationship between the donor's blood level of the enzyme—alanine aminotransferase (ALT) and the incidence of post-transfusion hepatitis (PTH) in recipients of that blood. The significant findings in the chart demonstrate the risk of hepatitis increases in proportion to the level of donor transaminase. If at least one donor had an ALT greater than 54 IU 1 then the risk of hepatitis was significantly greater than if all donors had an ALT less than that level.

NIH PHOTO 1719

hepatitis even though they received only blood with an ALT concentration below 45 IU. According to the NIH study, 9 percent of patients who received only blood with an ALT level of 53 IU or less acquired hepatitis.

Second, not all blood units with elevated ALT concentrations will cause hepatitis. In the TTV Study, about 60 percent of patients who received blood with an ALT above 45 IU did not get hepatitis, while in the NIH study, 72 percent of the 56 donors with elevated ALT levels were not associated with a case of PTH.

According to the NIH researchers, such imperfect correlations reflect the nonspecific nature of the ALT test and raise doubts about the wisdom of adopting donor ALT screening as a routine practice. While ALT screening might prevent 30 percent of PTH (90,000 cases per year in the U.S.), 70 percent will not be prevented, and even the prevention of 30 percent is in some doubt without further controlled clinical trials. Such screening would also increase the complexity and cost of blood delivery, as well as reducing the availability of donor blood, already in critically short supply. The potential blood loss from donor ALT screening has been estimated at more than 90,000 units per year in the U.S. alone. ALT testing would, in addition, cause an annual increase of $20 million in the cost of blood nationwide.

Another major problem with ALT screening of donor blood is that, due to the nonspecific nature of the test, a positive test result does not necessarily signify infectivity. Factors other than hepatitis infection can cause elevated ALT levels in a donor's blood stream. These factors include alcoholism, a variety of medications, toxins, other viral illnesses and certain congenital and immune liver diseases.

The question of whether ALT testing of donor blood should be implemented routinely is important and controversial. Because of its importance a panel of experts was convened to examine the issue in June, 1981. The panel's consensus was that available data were too inconclusive to warrant a policy decision at the present time, and they endorsed further study.

Until future research sheds more light on such subjects as the causes of ALT elevations in donor blood, the effect of ALT screening on blood supply, and the legal and financial ramifications of ALT testing, the controversy is liable to remain unresolved. In the words of the NIH researchers: "The ALT testing of donors is....in a tenuous balance between risk and benefit....adoption of donor ALT screening will, at best, be an interim measure. Continued vigorous pursuit of a specific serological test for the agent or agents of non-A, non-B is mandatory."

Reports of this research can be found in the August 7, 1981 issue of *JAMA* and the July 11, 1981 issue of *Lancet*. ■

Steroid Drug May Prevent Respiratory Distress Syndrome in the Newborn

Prepared by the National Heart, Lung and Blood Institute

Initial results of a major clinical study seeking to prevent neonatal respiratory distress syndrome (RDS) have been reported in the American Journal of Obstetrics and Gynecology.

Overall, the study data indicate that a synthetic steroid drug (dexamethasone) under certain conditions can prevent RDS in the neonate when administered to mothers who are considered to be at high risk of premature delivery.

Neonatal (newborn) RDS is a condition in which an infant's lungs have not developed sufficiently and therefore, are unable to process enough oxygen for the baby's needs even when the baby receives pure oxygen. Infants born prematurely are more likely to have RDS than are infants carried to term, but the underlying cause of RDS is not completely understood Up to 60 percent of premature infants have RDS and as many as 8-10,000 deaths among live born infants per year may be the result of RDS.

The study, called the Collaborative Study on Antenatal Steroid Therapy, was sponsored by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute (NHLBI). Four U.S. and one Canadian clinical centers participated. The work began in 1976 and will conclude in 1983 when the last baby born into the study has had final evaluation at three years of age.

This collaborative study was the result of a 1974 NHLBI workshop that recommended dexamethasone be evaluated for risks and benefits in premature deliveries. That recommendation was based on earlier animal studies showing that administering corticosteroids (the class of drugs to which dexamethasone belongs) late in pregnancy speeded lung maturity in the fetus resulting in more viable premature offspring.

The results indicated that dexamethasone can lower the incidence of RDS among premature offspring in cases of single deliveries. No effect was noted upon the incidence of RDS. Surprisingly, the beneficial effect was most pronounced among female infants. Approximately one out of every five girls born prematurely to mothers who were not treated with dexamethasone had RDS, whereas only one out of every 20 female babies had RDS if their mothers had received dexamethasone.

In contrast, one out of every six male babies had RDS regardless of whether their mothers had received dexamethasone. Another surprising result of the study has been that whites in general seem to benefit less (in terms of lowering the incidence of RDS) than do other racial/ethnic groups. Overall, no difference was observed in mortality between the dexamethasone group and the control group.

The apparent efficacy of dexamethasone in preventing RDS confirms results obtained in another large clinical study in New Zealand eight years ago and in some smaller, more recent studies in the U.S. However, the different response observed in the two sexes and in different racial/ethnic groups has not previously been reported.

The five participating clinical centers screened nearly 8,000 pregnant women at risk for premature delivery to find those eligible to be enrolled in the study. Two groups, comprising a total of 696 women, were formed. The control group consisted of women who received placebo (blank) injections. The experimental group consisted of women who received up to 20 mg of dexamethasone divided into four doses 12 hours apart. Some women (less than 25 percent) delivered before receiving three or more injections.

Immediately upon delivery and at specified intervals afterwards, the infants received a battery of tests to detect RDS and to answer questions about any short-term and long-term effects on the development of the infant. The last of the tests will be administered as each infant reaches 3 years of age.

To date, no short-term adverse effects of the drug have been found on the fetus, the newborn, or the mother.

The potential usefulness of dexamethasone in this application is limited by certain factors. For reasons still unknown, white male premature babies were not benefited at all by their mother's being given the drug. Also, twins and other multiple births did not show any less incidence of RDS in the treated group, and questions about the long-term effects of dexamethasone remain to be answered.

For these reasons caution is being advocated in the use of steroids to prevent RDS. Nevertheless, it is encouraging that this form of therapy has the potential to prevent at least 15,000 cases of RDS per year (based on female infants alone) and thus save in the order of $200 million for neonatal intensive care. ■

Enzyme Replacement: Emerging Treatment for Lipid Storage Diseases?

By Ray Fleming

The youngsters on the fifth floor of NIH's Clinical Center have been fighting a common enemy: a hereditary metabolic disorder known as Gaucher's disease. It has not been easy, but with the help of a treatment pioneered by Dr. Roscoe Brady, a leading neuroscientist at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), their health is now improving.

For some time, Dr. Brady and his fellow scientists have been trying to reverse the dangerous buildup of fatty compounds (lipids) that occurs in patients with Gaucher's and other lipid storage disorders such as Tay-Sachs and Fabry's diseases. The abnormal lipid accumulation can result in a variety of potentially life-threatening problems, including swollen organs, lost and damaged nerve cells, bone degeneration, and reduced numbers of platelets and white blood cells. The cause of the trouble is a genetically determined shortage of effective enzymes—proteins that normally break the lipids apart.

Dr. Brady believes his technique, enzyme replacement therapy, can eventually become an effective treatment. The strategy entails administering the missing enzymes to the patient, in somewhat the same way diabetics are treated to overcome their insulin shortage. But before the therapy can be considered successful Dr. Brady must first obtain enough pure enzymes, direct them to sites in the body where excessive amounts of lipids are stored, and in some cases move them through the blood-brain barrier—the wall of cells that prevents large molecules from entering the central nervous system.

There are ten known hereditary lipid storage diseases,* most of which cause extensive nervous system damage, mental retardation, and often death in young children. Most Tay-Sachs children, for example, live only 2 to 4 years; certain forms of Gaucher's and the rarer Niemann-Pick disease often claim the lives of patients by the age of 2.

Today there are tests, developed by Dr. Brady and other scientists, to diagnose hereditary lipid storage disorders in the adult, the child, and even the fetus. Healthy carriers of the disorders can also be identified, and genetic counseling is available, as well as pregnancy monitoring techniques. But large-scale prenatal

Dr. Roscoe Brady, NINCDS researcher, treats a patient with Gaucher's disease by replacing missing enzymes that will help break down the fatty lipids that build up in the child's body

NIH PHOTO 1720

screening presents logistical problems, and for many, abortion is not an option. So while the search for ways to prevent these disorders goes on, much promising research work is also aimed at treatment.

For much of his career Dr. Brady, now chief of NINCDS's Developmental and Metabolic Neurology Branch, has been in the forefront of research in prevention and treatment of the genetic lipid storage diseases. His discovery of specific enzyme deficiencies in several of these illnesses prompted the scientific community to try different ways to supplement the enzyme shortage.

Because of the difficulty of obtaining sufficiently large quantities of the necessary highly purified enzymes, Dr. Brady and other scientists originally attempted transplants of the spleen, liver, and kidney to provide a source of these enzymes. These organs are major sites of excessive lipid accumulation in the storage diseases, but their replacement with normal, enzyme-producing organs provided at best only temporary improvement in patients' conditions. In these cases, the lipid breakdown rarely extended beyond the transplanted organ itself, leading investigators to theorize that each type of tissue in the body makes only enough enzymes for its own needs.

Today's preferred approach—administering pure enzyme directly to the patient—had to wait until techniques for isolating enzymes from human tissue were developed. By the mid-1970's, Dr. Brady and others were extracting small amounts of purified enzymes from human urine and placentas. As their procedures improved, larger amounts of the proteins became available, and clinical tests of direct enzyme replacement therapy became possible on a limited basis. Dr. Brady and his fellow scientists began administering the purified enzymes to Tay-Sachs, Gaucher's, and Fabry's patients via the bloodstream.

The results of such enzyme replacement clinical trials up to now have been mixed. Some tests have succeeded in temporarily lowering the lipid level in the blood and liver storage sites, and overall the condition of a number of Gaucher's patients seems improved. However, little difference has been seen in patients whose symptoms involve the nervous system.

Scientists have discovered that the replacement enzymes, once administered, rapidly leave the bloodstream and enter cells and tissues in the body, but do not necessarily migrate to the areas where scientists want them to go: sites of high lipid concentration. In some cases, the placentally derived enzymes are lured away from areas with high lipid accumulation by other cells which find the enzymes' structure chemically attractive. Other studies have shown that the enzymes are being rebuffed at the blood-brain barrier, thus preventing them from reaching brain cells where lipids are accumulating.

But the work of Dr. Brady and his colleagues (NINCDS's Drs. John Barranger, F. Scott Furbish, Andrew Gal, Edward Ginns, Peter Pentchev, and Daniel Stowens) has produced some promising bright spots. In a recent trial conducted by Dr. Brady and others at the Clinical Center, eight youngsters with Gaucher's disease, treated on monthly and bimonthly schedules, showed general improvement in their health: the swelling of the liver, spleen, and other organs has stopped, and the blood platelet level has stabilized.

Successful replacement therapy on a large-scale basis, however, is still elusive. "I think our technology is on the verge of giving us the solutions we need," says Dr. Brady. "But until we can produce the required enzymes in much greater quantities and target them to specific areas, replacement therapy will have to be considered experimental."

For scientists studying hereditary lipid storage diseases, the emerging technology of genetic engineering could have special applications. Using recombinant DNA techniques, they may soon be able to employ bacteria to produce the large quantities of enzymes necessary to treat the disorders—and to produce them at an affordable price. Such mass-produced enzymes would have the additional advantage of being more amenable to specific storage-cell targeting procedures.

"With the revolution in genetic engineering," says Dr. Brady, "we might even expect to tailor the enzymes for distribution to critical areas where they now aren't drawn." In the meantime, NINCDS scientists are trying new ways to direct replacement enzymes to where they are needed. By actually modifying the basic molecular structure of placental enzymes, they hope to make them chemically attractive enough for the lipid-storing cells and tissues to draw them in.

But if enzyme replacement therapy is to be effective in treating the progressive cellular, motor, and mental damage caused by the storage diseases that involve the nervous system, the enzymes must ultimately penetrate the protective blood-brain barrier. Dr. Brady and his colleagues are now conducting studies of barrier modification in animals, which they hope can be applied to the problem. By introducing concentrated solutions of certain sugars into the bloodstream to the brain, they have been able to temporarily "shrink" the cells of the barrier, thus allowing enzymes to pass through to storage sites in the central nervous system.

For now, the clinical trials of replacement therapy continue, in spite of a limited supply of enzymes. Dr. Brady is optimistic about the chances for ultimate success.

"Compared to the status in a number of other disorders, we've come a long way in a remarkably short period of time. We've found the source of the problem and can diagnose it, even before birth. I believe that we are close to successful treatment too!" ■

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*Gaucher's, Niemann-Pick, Fabry's, Tay-Sachs, Sandhoff's, Farber's, and Krabbe's diseases, metachromatic leukodystrophy, fucosidosis, and generalized gangliosidosis

Study Shows Babies of Smoking Mothers do Poorly in Tests given at Birth

By Susan Gerhold

Statistics compiled by the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) show that women who smoke more than one pack of cigarettes a day reduce their chances of delivering a healthy, well-developed baby.

Researchers at the University of Michigan's Center for Human Growth and Development and the Pediatric Neurology Section are working with the data gathered by the NCPP through grants and contracts supported by the Institute.

During the 1950s and early 1960s, the NCPP followed 50,000 women through their pregnancies, studied their health, recorded their habits, and then examined, tested, and observed their babies for seven years after delivery. Much of the information gathered by the NCPP is being evaluated by the Michigan researchers in studying the relationship between the extent of women smoking during pregnancy and the proportion of low or depressed Apgar scores.

Apgar scores measure the infant's ability to survive the transition to the outside world. Based on the NCPP data, Apgar scores were strikingly lower among full-term and pre-term infants born to mothers who were heavy smokers. Somewhat lower scores were recorded from babies born from moderate smoking mothers as well.

Stanley Garn and his colleagues at the Center for Human Growth and Development noted that women smoking two to three packs of cigarettes a day delivered babies who did four times as poorly in the Apgar scores than babies whose mothers did not smoke.

When reviewing data on babies with gestation of 38 weeks or longer, test results showed that the Apgar scores were again lower, especially in babies whose mothers smoked two to three packs of cigarettes a day.

The NCPP researchers gave Bayley Behavioral tests to the infants at 8 months of age. The results showed that babies born to smoking mothers did not do as well as babies born to non-smoking mothers. These results, according to Garn, suggest that "maternal smoking during pregnancy continues to show its effects long after birth, even though it is to a lesser degree."

When examining the data on the babies whose mothers smoke, the researchers found that the babies had elevated hemoglobin and hematocrit levels that seem to increase in proportion to the extent of the mother's cigarette usage. They also noticed that smoking mothers have higher levels of carbon monoxide in their blood stream, suggesting that the baby not only is being exposed to carbon monoxide poisoning, but suffers from hematological problems as well—two factors the Michigan researchers say may influence the lower than normal Apgar scores.

"The Effect of Maternal Cigarette Smoking on Apgar Scores" was published in the *American Journal of Diseases in Children*, Volume 135, June 1981.

For more information contact the National Institute of Neurological and Communicative Disorders and Stroke, Office of Scientific and Health Reports, NIH, Building 31, Room 8A06, 9000 Rockville Pike, Bethesda, Maryland 20205. ■

Physicians urge their patients not to smoke while pregnant. Studies continually show that babies born to smoking mothers do poorly on behavioral tests given at birth.

NIH PHOTO 1721

NIAID Study Identifies Factors that Affect Outcome of Kidney Transplants

By Bobbi Bennett

Transplants from living relatives are known to be far more successful today than the more frequently performed ones that use kidneys from cadavers. According to the National Institute of Allergy and Infectious Diseases (NIAID) study, known as the Kidney Transplant Histocompatibility Study (KTHS), 73 percent of the kidneys from living related donors still functioned one year after implantation. In contrast, only 49 percent of those from cadavers did. Equally impressive was the fact that during the first year, death of the recipient occurred in only 10 percent of the former, but in 19 percent of the latter.

Transplantation also appears to promote patient rehabilitation. Of those with grafts still functioning after one year, 94 percent of the recipients of living-donor kidneys and 89 percent of those with cadaveric ones were engaged in full-time activity. Fewer than 30 percent of dialysis are reported to be employed full-time and only 17 percent, part-time.

To investigate the factors responsible for such differences, NIAID collected data from more than 40 medical centers concerning 2418 transplants which were performed between 1974 and 1976, although follow-ups continued through 1978. About 37 percent of the transplanted kidneys came from living relatives of the recipients; the remainder came from unrelated persons who died suddenly, usually as a result of head injuries.

The NIAID study correlated the transplant outcomes with the characteristics of the donors, recipients and treatments using tables for graft and patient survival. The initial objective of the study was to determine what effect, if any, matching of donors and recipients for HLA-A and HLA-B histocompatibility antigens had on the probability of long-term graft survival. Analyses of the data indicate that tissue typing does not appear to be a very significant factor in predicting the outcome of cadaveric transplants, a sharp contrast to the situation with living-donor ones. However, an association of reduced graft survival with stimulation in the mixed lymphocyte culture (MLC) raises the possibility that a positive MLC might be a clear contraindication to the to the use of a kidney from a living donor.

One of the major current thrusts in kidney transplantation is to develop guidelines for blood transfusion of the recipients of kidney transplants. The KTHS data verified the well-known beneficial effect of blood transfusions prior to transplantation. Six to 10 transfusions appear to be the optimal number of units whicn can increase one-year graft survival by almost 20 percent.

The KTHS analyses also addressed the related question of whether blood transfusions given during or very shortly after cadaveric kidney transplants improve graft survival. These were found to have a minor but detrimental effect on kidney transplant outcomes.

A very dramatic improvement in graft survival from a cadaver was seen when the patient's spleen was removed prior to receiving the kidney transplant. The diseases that cause kidney failure were also found to affect the outcome of transplantation. Patients with pyelonephritis—inflammation of the kidneys—have a greater than average graft survival, whereas those with nephrosclerosis—vascular disease of the kidney—due to hypertension or diabetes have a poorer than average graft survival. Other significant factors such as the patient's race, age, and pharmacologic immunosuppression, were also identified.

Because of the many factors that appear to affect acceptance or rejection of the graft, a major effort was devoted to the development of a multivariate statistical model which would permit identification of those risk factors that are truly independent and significant. This task was carried out for the NIAID by the Naval Medical Research Institute. The importance of this approach is illustrated by the fact that conventional life-table analyses failed to detect a difference in graft retention between initial transplants and retransplants. When the statistical model was used to correct for the effects of pretransplants blood transfusions, a highly significant reduced success rate of retransplants was revealed.

Another important outcome of the application of statistical modeling and multivariate analyses is calculating and assigning weights to the various risk factors. Once these weights are available, it is possible to estimate the probability of graft retention to any reasonable time after transplantation, and to compare these probabilities for potential recipients subject to various risk factors.

The following example illustrates how the predictive model can be used. The waiting lists for cadaveric kidneys are quite long due to the large need but drastic shortage of available kidneys. Often, cadaveric kidneys are transported substantial distance. Because prolonged storage time of the kidney is a factor associated with decreased graft survival, a trade-off may be necessary between a recipient with a poorer prognosis who is nearby and a better candidate who is farther away. Another factor associated with decreased graft survival is the age of the recipient. However, the NIAID model predicts that the chance of graft survival in a 45-year-old recipient who can be transplanted within 10 hours of receiving the cadaveric organ equals that of a 25-year-old for whom a delay of 45 hours would be required.

The validity of this approach is totally dependent on the quality of the information from which the weights of the risk factors were calculated. The KTHS is the most searching and comprehensive study currently available, and very great efforts were made to ensure the accuracy of the data. However, the weights of the risk factors must be verified through a comparable analysis of independent arrays of information on kidney transplantation. This is presently being carried out.

Enhancing the success the kidney transplantation is highly desirable from both medical and economic points of view. The costs for kidney transplantation and maintenance dialysis in the U.S. are borne by the Federal government through the End Stage Renal Disease program.

Most of the current $1 billion annual tab for this pays for the dialysis of an estimated 45,000 individuals, a group that is projected to increase by 9000 per year. ESRD also pays for the more than 4000 renal transplants performed here annually. The cost in the first year for these patients, including that of the transplant, is $29,000—approximately that of one year of dialysis. However, if the graft continues to function, this figure drops to $1000 in subsequent years.

Since about half of the patients on dialysis are likely to benefit from transplantation, the provision of objective estimates of the probability of success of renal transplants should represent a useful advance in the management of patients and should help the physician and his or her patient in making critical choices and decisions.

For a qualitative summary of the analysis of the KTHS, contact Dr. Henry Krakauer, Genetics and Transplantation Biology Branch, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20205 or phone 301/496-7551. "The Kidney Transplant Histocompatibility Study, Analysis of the Data; Phase One: An Overview" may be purchased from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402 for $28.00. The GPO stock number is 017-044-00036-2. ■

Sodium Transport Found to be an Effective Diagnostic Tool for Essential Hypertension

By Susan Gerhold

A simple laboratory test to identify persons who have or will develop essential hypertension (high blood pressure of unknown cause, found in almost nine percent of the general population) may result from research on red blood cell membranes.

Hypertension, one of the most common cardiovascular diseases, affects millions of people each year and kills at least 250,000 Americans annually. Approximately 95 percent of the people who suffer from high blood pressure have essential hypertension. The other five percent have secondary hypertension—high blood pressure that usually results from another illness, such as kidney disease, but may sometimes occur as an unwanted side-effect of certain medications.

Drs. Daniel Tosteson and Mitzy Canessa and their colleagues at Harvard Medical School, working under a grant from the National Institute of General Medical Sciences (NIGMS), found that a transport system that normally carries sodium in and out of the red blood cells is twice as active in individuals with essential hypertension as in individuals with high blood pressure secondary to another disorder. This finding may lead to the development of a simple laboratory test that will enable a physician to pinpoint the type of hypertension a patient has, without submitting him or her to extensive testing.

Sodium, which is found in the blood stream and surrounding red blood cells, can be transported back and forth across the cell membrane through several pathways. When the element lithium (which is not normally present) is added to red blood cell samples in laboratory tests, lithium is also transported across the cell membrane through one of these same pathways, in exchange for sodium. The Harvard researchers noted that blood samples taken from the essential hypertension patients showed a sodium-lithium transport system that was twice as active as that in the normal control subjects.

Comparison studies were then done on the sodium-lithium activity in red cell samples taken from asymptomatic relatives of eight patients with essential hypertension and from 10 normal volunteers. Results showed that the transport rate of sodium-lithium was almost twice as high in the relatives as in the normal controls. According to the researchers, this finding may help physicians identify family members of patients with essential hypertension who may be at risk of developing the disorder. Further research is planned to follow the relatives of essential hypertensive patients over time, to see if there is a correlation between their test results and eventual development of hypertension.

The cause of the increased rate of sodium-lithium transport in the essential hypertension patients and their relatives is unknown; however, Canessa and Tosteson theorize that red blood cell membranes in these individuals may have an increased number of transport sites permitting passage of sodium in and out of the cells.

The relationship "between red blood cell transport and hypertension may not be directly causal," Dr. Canessa noted, but the study may lead to a discovery of a similar transport disorder in other types of cells more directly associated with hypertension—for example, the smooth muscle cells (elongated and contracting vascular cells) in the walls of the small arterial branches.

In the future, researchers will be exploring whether the transport disorder is itself the cause of hypertension or is secondary to the true cause.

For additional information on this research, contact Dr. Tosteson or Dr. Canessa at Harvard Medical School, Boston, Massachusetts. ■

Increased Risk of Heart Attack Found in Former Long Term Pill Users

By Maureen Gardner

Women who use oral contraceptives for 5 years or longer carry an increased risk of heart attack which persists at least 9 years after pill use is stopped. This finding comes from the first study large enough to uncover such a relationship, and the investigators warn that the data should be interpreted with caution until the results are repeated elsewhere.

Directed by Dr. Dennis Slone, a research team from the Boston University School of Medicine, the Harvard School of Public Health, and the University of Pennsylvania School of Medicine surveyed the coronary care units of 155 h[illegible]pitals. They located 556 women between the ages of 25 and 49 with first episodes of heart attack, and compared the medical and drug use histories of these women with those of 2,036 age-matched controls.

In line with earlier reports, the researchers found that current use of oral contraceptives increases the risk of heart attack three to four times. The new finding is that the risk for long-term users, those on the pill for 5 years or longer, does not reverse once pill use is stopped. It can remain as much as three times higher than the normal risk for at least 9 years, and further research may show that it lasts even longer.

Overall, former pill users in the study had only a 20 percent greater chance of heart attack than did women who never used the pill. The added risk was far from evenly distributed, however. An analysis from the length of time of pill use showed that women who used the pill for less than 5 years had no added risk; those with 5 to 9 years of pill use had a 60 percent greater chance of heart attack; and those with 10 or more years of use had two to three times the normal risk. Because of the scarcity of data for younger age groups, this analysis was limited to women aged 40 and older.

The higher risk was found even in lo[illegible]term users who had stopped taking the pill up to 9 years earlier. There were too few subjects who had been off the pill for 10 or more years to indicate whether the risk continues beyond the 10-year post-pill interval.

While some of the large studies on the pill have shown an increased risk of heart attack in current users, it was not previously feasible to perform the kind of detailed analysis found in this project. In other studies there simply were not enough heart attack cases to analyze. This is because even in a high risk group of pill users, heart attack is still rare: it occurs in an estimated 9 in 10,000 pill users between the ages of 40 and 44.

The investigators note that the link between past pill use and heart attack points toward mechanisms that involve clogging of the arteries, or atherogenesis. Because of the pill's established effects on certain functions that affect the health of the arteries, including lipoprotein metabolism, glucose tolerance, and blood pressure, the researchers believe that accelerated atherogenesis might be expected. However, it is not certain whether these side effects alone are responsible for the increased risk this study revea[illegible]

This research, which was funded in part by the National Institute of Child Health and Human Development (NICHD), was reported in the *New England Journal of Medicine*, Volume 305, Number 8. ■

NINCDS Scientists Search for a Protein that Can Help Diagnose Nervous System Disorders

Prepared by the National Institute of Neurological and Communicative Disorders and Stroke

A protein-detecting microtechnique to help diagnose neurological disorders such as multiple sclerosis, myasthenia gravis, and Guillain-Barre syndrome has been developed by scientists from the National Institute of Neurological and Communicative Disorders and Stroke, the National Cancer Institute, and several cooperating institutions.

The new microtechnique relies on a standard procedure, electrophoresis, and a chemical combination of a polyacrylamide substrate with a sodium dodecyl sulfate (SDS-PAGE) suspension to detect a form of the protein immunoglobulin in extremely small amounts of unconcentrated cerebrospinal fluid.

In at least 10 nervous system disorders, the presence of this protein form in CSF is considered a diagnostic characteristic.

In electrophoresis, proteins in a liquid suspension move across an electrically charged substrate made of paper, starch, or other substances. During this movement, different proteins separate on the substrate into identifiable bands according to their individual reactions to the electric field.

Previously, the standard electrophoretic method for detecting immunoglobulin in CSF used an agar substrate and required relatively large amounts of CSF, which had to be concentrated 50 times or more. The process used to concentrate CSF was suspected of making test results difficult to interpret.

A more recent procedure using polyacrylamide and SDS-PAGE detected the protein in unconcentrated CSF, but still required considerable quantities of the fluid.

The new microtechnique largely eliminates these problems. The test not only requires much less CSF from patients, but is more sensitive than the standard electrophoretic technique.

Immunoglobulin has been detected in 94 percent of the previously diagnosed multiple sclerosis patients examined by the microtechnique; only 76 percent of the same individuals tested positively for the protein with the standard process.

The new detection procedure has now been recommended for routine diagnostic use. The lead investigator of this study was Dr. Matti V. Iivanainan, now of the department of neurology, University of Helsinki. ■

Immediate Treatment can Save Comatose Patients with Hematomas

By Helen Ou

Operating on patients with acute subdural hematoma (ASDH), a severe head injury, within four hours of injury could mean the difference between life and death, according to researchers at the Medical School of Virginia. The high death rate has led researchers to examine various factors that could reduce the 60 to 90 percent mortality rate associated with this type of injury.

The researchers found in reviewing the records of 82 comatose patients with traumatic ASDH that the patients who underwent surgery within four hours of injury had a mortaility rate of 30 percent. In contrast, the study showed a 90 percent mortality rate in patients who had surgery after four hours. Apparently, the prompt surgical removal of the intracranial hematoma (blood clot) helped to decompress the brain, thereby reducing the adverse effects of secondary brain damages common to this type of injury.

This retrospective study covered an eight-year period, and included 62 men and 20 women. An average of 5.4 hours elapsed from injury to surgery. However, patients who recovered with moderate disability averaged closer to 2.8 hours of delay. Seven patients in the group were severely disabled. Men had a higher mortality rate than women. According to the researchers, the lower mortality rate of women was due to earlier surgery, averaging about two hours earlier than men.

The study revealed that rapid transport of patients with ASDH to a hospital equipped for prompt diagnosis and surgery was also a very important factor in reducing the high mortality rate.

Initial neurological tests were given by stimulating the motor, pupillary and oculomotor area of the brain and recording the responses electrically through brain waves. Through this process, brain dysfunction could be assessed in each patient. These electrical studies proved to be a good prediator of outcome for ASDM patients. In this study, all patients with severely abnormal brain dysfunction died. In some cases, the severity of the injury could be the determining factor in the outcome, and not necessarily the time lapse before surgery.

A danger in an ASDH injury is the increase in intracranial pressure and brain swelling, which could result in irreversible brain damage. The speed with which surgery is undertaken to remove the hematoma is important because the brain can withstand compression for only a limited time without damage. Also, brain swelling often develops after removal of the hematoma, and if this secondary swelling is not controlled, the pressure within the skull can become greater than the blood pressure, causing the brian to die from lack of blood. There is no effective treatment for these secondary processes. The study suggests that the use of dehydrating agents such as manitol or other diuretics which might be effective in lowering the pressure.

Postoperative intracranial pressure was monitored in all patients for at least three days. After surgery, progression of the secondary injury resulted in uncontrollable brain swelling in 24 percent of the patients, despite vigorous medical treatment. It would appear that earlier surgery could help prevent preoperative increased intracranial pressure and the development of the secondary injury.

The most important factor influencing the outcome of patients appears to be surgery within four hours of injury. The researchers suggest that this finding, along with rapid transport of patients to a hospital capable of providing prompt diagnosis and surgery, could reduce the high mortality rate associated with ASDH.

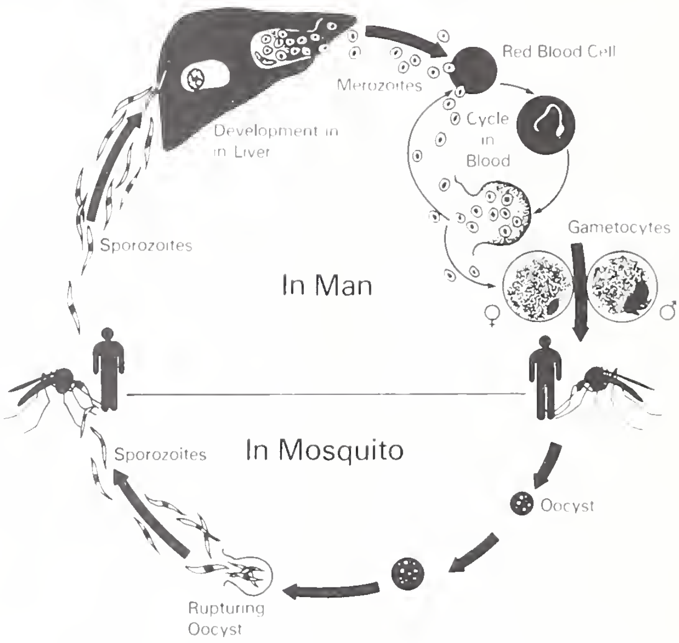
Further studies may be needed to answer questions such as: Should comatose patients be transported to the closest hospital or to a more distant one, better equipped to treat these type of injuries? How much treatment should be given to patients in transit to a hospital? Answers to these questions could further influence the outcome for ASDH patients, and thereby reduce their high mortality rate.

This study was supported in part by a grant from the National Institute of Neurological and Communicative Disorders and Stroke, and was reported in the June 18, 1981 issue of the *New England Journal of Medicine.* ■

Malaria and Schistosomiasis: Parasitic Diseases that Continue to Plague the World's Population

By Susan Gerhold

Malaria Life Cycle



The life cycle of malaria starts with the infected mosquito. The mosquito injects sporozoites into the blood stream which then localizes in the liver cells. The parasites develop into merozoites, that rupture and invade red blood cells. The parasites then reproduce asexually into merozoites, and continue to invade additional red blood cells. At this stage the infected person becomes ill. However, the cycle continues, the asexual parasites develop into sexual forms called gametocytes and develop oocysts in the mosquito's gut. The sporozoites develop and inject into man and the whole cycle begins again. **NIH PHOTO 1722**

Malaria—a disease that has been eradicated in the United States, still plagues countries in Latin America, Africa, and Asia. Schistosomiasis, a lesser known parasitic disease, affects more than 200 million people throughout the tropical regions of the world. Both of these parasitic diseases are currently being studied at the National Institute of Allergy and Infectious Diseases (NIAID), and investigators hope to find suitable vaccines since the diseases show resistance to drugs and insecticides, and control measures are inadequate.

Franklin A. Neva, chief, Laboratory of Parasitic Diseases (LPD), NIAID, told an audience of science and medical writers attending a NIH-sponsored science writers seminar recently, that finding a vaccine against parasitic diseases is not a simple task, due to the complex-life cycles of the infecting organisms and their great ability to evade attacks from the body's immune system.

According to Neva, a vaccine may eventually be found because of the "rapid advances in immunology and molecular biology during the last decade."

Malaria is transmitted by an infected mosquito. The mosquito injects sporozoites into the blood stream which then localize in the liver cells. The parasites develop into merozoites which rupture from liver cells and invade the red blood cells. Within the red blood cells the parasite reproduces asexually into merozoites which invade additional red blood cells, resulting in clinical disease. A percentage of the asexual parasites develop into sexual forms called gametocytes, which are infectious to mosquitoes for transmission to others. The gametocytes develop into oocysts in the mosquito gut and then into sporozoites. The sporozoites are injected into man and the whole cycle begins again. In most cases, the victim suffers from flu-like symptoms: malaise, headache, fatigue, chills, and fever. If not treated, one type of malaria can lead to death.

Schistosomiasis is especially found in countries using irrigative agriculture—a situation which produces increased aquatic breeding sites for the fresh water snails that are involved in transmitting the disease to man. A debilitating infection, the victim becomes infected through wading, bathing, or washing clothes in fresh waters where the snails' cercariae (free swimming larva) are found. The cercariae burrow in the skin and then move through the blood stream and mature into worms—migrating to the liver, and then to the bladder, or intestines. The victim suffers from chronic diarrhea, cystitis, fever, and general fatigue. Some of the eggs from the adult worms are eliminated in the feces or urine, but others are trapped in the infected person, damaging the tissues of the liver, intestine, or bladder.

Investigators have found that both diseases produce natural immunity, however, schistosomiasis' natural immunity is less clear than it is in malaria. It has been found that in countries where malaria is prevalent, children are infected early and repeatedly, and if they manage to survive, they seem to develop solid immunity to reinfection.

Dr. Louis H. Miller, Head of the Malaria Section, NIAID, stated that the only malaria vaccine that has been successful in man has been the sporozoite vaccine under highly experimental conditions, and this vaccine attacks the stage of the parasite that is injected by the mosquito and blocks liver infection. However, this vaccine requires large numbers of sporozoites irradiated with x-rays (weakened), repeated inoculations, and immunity only lasts for three to six months—all obstacles to a mass vaccination program.

Miller also described the most recent advances using monoclonal antibodies. He stated that researchers at New York University have identified the antigen on the sporozoites to which effective immunity is directed in rodent and primate malarias. It is hoped in the future that comparable antigens will be identified in human malaria. Currently, investigators face the problem of identifying the gene for this protein so it can eventually be synthesized in recombinant DNA systems.

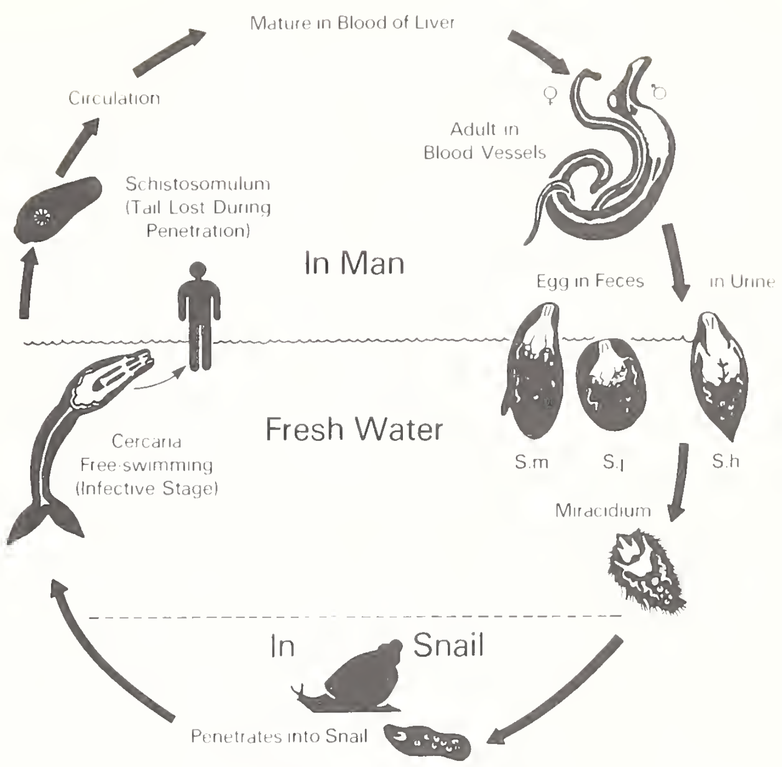
NIAID researchers here in Bethesda are currently studying receptors on red blood cells for malaria parasites. The parasite s to attach to a receptor on the red blood cell in order to subsequently invade this cell. The researchers speculate that after the merozoites attach to the red blood cell receptor they release a substance into the red cell membrane, which enables the parasite to enter the cell. Different malaria parasites, according to Miller, attach to different receptors on red blood cells of the same host species. It has been shown that blacks cannot be infected by *P. vivax*, one type of human malaria, because one of their blood group antigens is different, but they can be infected by *P. falciparum*. The receptor for *P. falciparum* is different from *P. vivax* and consists probably of glycoproteins on the red blood surface. Using this information, researchers hope to block recognition by the merozoites of the red blood cell receptor using chemical or immunologic means targeted against either the red cell or merozoite surfaces—thereby arresting infection.

Schistosomiasis, on the other hand, could be controlled if an effective vaccine were administered early in childhood and designed to provide lasting protection against infection. A vaccination program of this type, according to F. Alan Sher, head of the Cell Biology and Immunology ection, NIAID, "would alleviate the need r subsequent therapy, and by means of a vaccine, could be controlled without disrupting either the ecology or culture of the local community."

LPD researchers examine schistosomiasis patients from all over the world at NIH's research hospital. Some of the patients arrive in the United States from Puerto Rico, or Laos, and some are Action (Peace Corps) volunteers, suffering from this parasitic disease. NIAID scientists and grantees are working on determining why some individuals are affected by schistosomiasis and others are not. They are also studying the behavior, physiology, and biochemistry of the parasite itself. In order to develop an antischistosomal vaccine, the researchers need to know and acquire a thorough understanding of the human immune response to schistosome worms and the mechanisms by which susceptible individuals can be made immune to them.

The NIAID researchers seem to share the idea that vaccines are possible but that a vaccination program may not be the answer. Therefore, multiple approaches to control malaria and schistosomiasis (such as vector control, more effective drugs and health education) need to be rsued.

Life Cycle of Schistosomes



The life cycle of the schistosomes starts in the fresh waters where snails are involved in transmitting the disease to man. The victim is infected by wading in the fresh waters where the snail's cercariae are found. This free swimming larva burrow in the skin and then move through the blood stream and mature into worms—migrating to the liver, and then to the bladder or intestines. **NIH PHOTO 1723**

The victim of schistosomiasis suffers from chronic diarrhea, cystitis, fever, and general fatigue. Some of the eggs from the adult worms are eliminated in the feces or urine, but others are often trapped in the infected person, damaging the tissues of the liver, intestine, or bladder. **NIH PHOTO 1724**

The article "No Direct Cause and Effect Found Between Low Blood Cholesterol and Cancer" was identified incorrectly in last month's News and Features. The paper was prepared by the National Heart, Lung, and Blood Institute. Our apologies to everyone involved.

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

Ms. Maureen Napper
National Institutes of Health
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Ms. Maureen Napper:

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NIH PHOTO 1725

News&Features
from NIH

November 1981

"Runners' high" has been a recognized phenomenon among athletes, but with no confirmed physiologic basis. Now, NIH-supported researchers at the Mass General Hospital have shown that an opium-like hormone is secreted in the blood during regular, vigorous exercise. This finding could explain why some people don't seem to notice injuries during strenuous exercise. See page 4.

Physicians have recently identified a rare type of cancer in homosexual men that seems to be linked with their lifestyle. If a clear association can be made, prevention may be possible. A group of investigators at several institutions—headed by the NCI—are planning a research program to study the many factors involved in this unusual disorder. See page 8.

Science's most prestigious award was given to two NIH-supported researchers, both professors of neurobiology at Harvard Medical School. Their research has changed our view of how the brain processes signals sent to it from the eyes. Their findings have influenced treatment of congenital cataract and other blinding or vision-distorting conditions in children. See page 7.

Sexual intercourse during late pregnancy is not harmful to the fetus according to a study by NICHD researchers. The outcome of 10,477 pregnancies showed that women who had intercourse during the last trimester had no increased risk of complications. Various smaller studies have attempted to assess the risk of intercourse in late pregnancy, but with conflicting results. See page 3.

Computers are being used to study inherited diseases among groups of individuals, like the Mormons, with well-documented genealogical information. Supported by the NIGMS, the project will assist researchers in identifying families in which certain diseases seem to cluster. This modern approach to disease research may eventually result in predicting and preventing disease in predisposed individuals. See page 2.

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Research Project Uses Computer to Study Inherited Diseases Among Mormons

By Doris Parker

In 1847 a Mormon pioneer arrived in Utah, married four wives and set up a prosperous household. But he gave many of his children (the average for that day was eight children per wife) an unusual inheritance: a gene for a rare metabolic disorder called Wilson's disease.

Wilson's disease, in which patients fail to eliminate copper from their bodies, causes anemia, liver damage, brain damage and sometime death. Inheritance of a gene for the disorder from both parents is necessary for the disease to develop.

Today the pioneer's 4,000 descendants constitute one of the largest populations of Wilson's disease (including asymptomatic people carrying only one gene for the disease) being actively studied in the world, according to Dr. Mark Skolnick, head of a unique genetic research project.

The project, supported by the National Institute of General Medical Sciences (NIGMS), will establish a computer resource for genetic epidemiology using data from the Utah Mormons. Wilson's disease is only one of dozens of diseases that are being studied or are proposed for study.

Polygamy in the early days of Mormon settlement, high fertility, and population stability all make the Utah population ideal for epidemiological studies. Moreover, much crucial genealogical information has already been gathered. For 140 years, the Mormon church has encouraged members to compile personal family trees and record them with the Genealogical Society of Utah. The result is the single most comprehensive repository of genealogical data in the world, incorporating nearly 8 million family trees. Dr. Skolnick hopes to include, in his studies, some 200,000 families with at least one ancestor in the original pioneer group.

The diseases proposed for investigation range from Huntington's disease, where there is a clear-cut pattern of dominant inheritance (only one gene from one parent needed to develop the disease), to cancers that may be associated with heredity in a variety of ways.

"Powerful, inexpensive computers now permit exploration of complex models that include both genetic and environmental components," Dr. Skolnick says. His group has developed a computer program, "GENISYS", that allows researchers to ask questions and analyze data without having to use a computer language.

Many sources of information will be combined with the basic genealogical data, including hospital discharge records, death certificates, records from the Utah State Tumor Registry, and similar data. With this information the computer can identify families in which certain diseases seem to cluster.

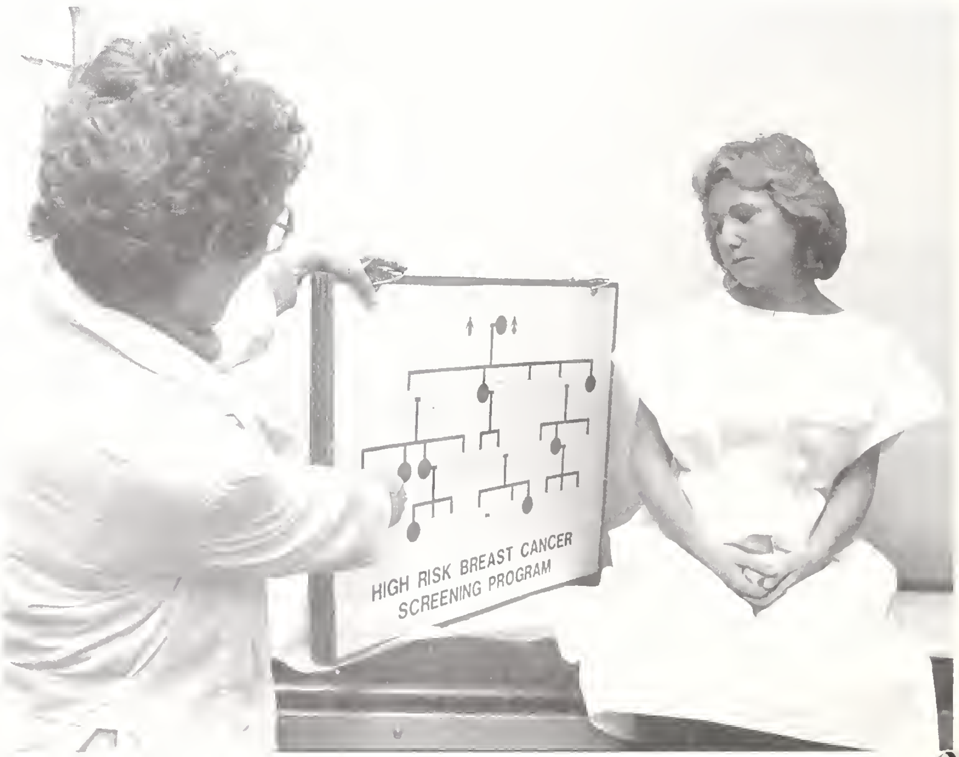
The computer can indicate if the disease seems to be inherited in a dominant, an intermediate or a recessive manner. Disorders in which individuals carry one gene for the disorder and show only mild symptoms of it are said to be inherited in an "intermediate" mannner. Those that are inherited in a recessive manner require a gene from both parents for the disorder to develop.

When family disease clusters are identified, Dr. Skolnick's group can collect additional information that will help shed more light on the disease under investigation. For instance, questionnaires can help identify enviromental factors that may be necessary, in addition to hereditary factors, for the disease to develop.

One way to "get a handle" on the nature of a genetic disorder, Dr. Skolnick points out, is to find another trait that seems to be inherited with the disease. For instance, if a person with a particular disease always lacks a certain protein in his or her blood, then researchers can explore the possibility that the protein may be directly involved in the disorder and thus come closer to a treatment or cure.

Even if the missing protein is not directly involved in the disease, its absence can indicate that the individual is asymptomatic but may later get the disease. Then early treatment and special precautions—such as low copper diet in the case of Wilson's disease—may save lives and limit disability.

A characteristic which is always inherited with another is said to be "linked" to that characteristic. This means that the genes for the two characteristics are located near each other on the same chromosome. To look for possible linkages in families at risk for a particular



The high risk breast cancer clinic sees about 300 family members a year. Researchers hope to locate the gene responsible for predisposition to the cancer so high-risk persons can be closely watched. The clinic is sponsored by the Utah State Division of Health.

NIH PHOTO 1726

Dr. Mark Skolnick studies only one-eighth of a pedigree for a Utah family that has a high incidence of breast cancer. Approximately 90 cases have already been identified and several hundred residents of Utah have inherited the gene. NIH PHOTO 1727

disorder, Dr. Skolnick's group collects specimens of blood and tissue to determine traits that family members at risk may have in common.

"We may attend family reunions," he says, "and after lunch we set up our blood-drawing equipment in the corner and add a whole new dimension to the occasion."

In addition, recombinant DNA technology is being used to learn the chromosomal location of genes that may be linked to diseases. This "mapping" of genes can provide many clues to the causes of inherited disorders. The linkage studies, using the Utah data base, are being supported by a separate NIGMS grant.

Dr. Skolnick's group has successfully proved that hemochromatosis, a metabolic disorder in which the body is unable to eliminate iron, is linked to a particular type of antigen (HLA) produced by body tissues. The iron overload resulting from the disorder causes cirrhosis, bronze skin, abdominal pain, and many other serious, and even potentially fatal, conditions.

The HLA linkage finding has led to discovery of several new cases of hemochromatosis in individuals who are asymptomatic and who will now be treated early to minimize the effects of the disease.

Cancer is a disease—really a whole collection of diseases—which provides a great challenge to the genetic researcher. Some cancers are clearly inherited, others seem closely connected with environmental conditions, and many appear to arise sporadically. Because the Utah Mormons have a lower incidence of cancer than the U.S. population as a whole, clustering of cancer in families, indicating possible genetic predisposition, tends to stand out.

Dr. Skolnick's group has been studying cancer for years. They have discovered that certain types of cancer are associated in families—for instance, families with a higher-than-normal incidence of breast cancer often also have high incidences of ovarian and prostate cancers. Colon, stomach and rectal cancers also appear together with greater than normal frequency in families.

Dr. Skolnick says, "The fact that this pattern of coaggregation is fairly consistent among and between most of the breast/reproductive and digestive cancers seems to suggest a common familial epidemiology for these cancers, with only a few exceptions."

The computer has also been able to determine certain risk factors for diseases such as breast cancer. For example, mothers who have their first children relatively late seem to be at increased risk for breast cancer. This suggests that late age at first delivery "enhances the genetic pathway, aiding in tumor initiation or growth," says Dr. Skolnick.

The kind of work Dr. Skolnick and his co-workers are doing is really just getting started, but the future is bright. "Modern medicine may become the art of predicting and preventing diseases in predisposed individuals," he says, "rather than attempting heroically to prolong life after irreversible damage has begun." ■

NICHD Study Challenges Theory That Coitus During Late Pregnancy is Harmful to Fetus

By Jody Dove

Despite a widespread belief that sexual intercourse during late pregnancy is harmful to the fetus, a study by researchers at the National Institute of Child Health and Human Development (NICHD) has found no evidence to support the claim.

Previous studies have suggested that sexual intercourse during the last three months of pregnancy could cause premature rupture of membranes, pre-term birth, a slowing of fetal heart rate or infection in the amniotic fluid surrounding the fetus.

The study, by James L. Mills, M.D. and Ernest E. Harley of NICHD and Susan Harlap of Hebrew University in Jerusalem found that intercourse did not increase the risk of these complications.

In a recent article in the English medical journal, *Lancet*, Dr. Mills and his colleagues wrote that, although the belief is widespread that intercourse is harmful in late pregnancy, little evidence exists to support the view. Obstetric textbooks of the 1950's, which warned doctors to discourage intercourse, cited no evidence to support their claim that intercourse could cause premature births and infection. Various small studies have attempted to assess the risk of intercourse in late pregnancy. The results of these studies have been conflicting and have been marred, according to Dr. Mills and his colleagues, by "small numbers, inappropriate choice of controls, failure to take into account confounding variables such as age and parity, or other methodological shortcomings."

The NICHD study was based on interviews with 10,477 women who had low-risk pregnancies and who delivered their babies between November 1974 and December 1976 at the three largest obstetric units in Jerusalem. Most of the women were between the ages of 21 and 35; the median education level of the group was 12 years. Forty percent of the women were in the hospital for their first delivery.

Although the study's main purpose was to gather data relating fetal outcome to prior contraceptive use, the mothers were asked about sexual activity during pregnancy. Each was interviewed the day after delivery and an obstetric history was obtained. To prevent study bias, the interviewers were not aware of the outcome of the pregnancy unless it was a stillbirth. Outcomes were determined through reviewing case notes after the mother and baby were discharged from the hospital. Additional data on obstetric complications were derived from examination of labor room log books.

The following are percentages of study participants having intercourse during pregnancy: first month, 90 percent; second month, 87 percent; third month, 90 percent; fourth month, 95 percent; fifth month, 95 percent; sixth month, 94 percent; seventh month, 89 percent; eighth month, 66 percent; and ninth month, 36 percent. The researchers said findings were similar to those reported for pregnant women in the United States.

The study found that women who abstained from intercourse in the last trimester of their pregnancies were older, less educated, from a lower social class, and tended to have had other pregnancies.

While women abstaining from sexual intercourse had more unfavorable outcomes in the seventh and eighth months, the differences between these and women who abstained were almost eliminated by adjusting for maternal age.

The researchers concluded that women who had intercourse during the last trimester of pregnancy had no increased risk of premature rupture of membranes, low birth weight, pre-term delivery, or perinatal death at any gestational age. Data from the study also showed that intercourse in one month did not produce any delayed, harmful effect on the pregnancy in succeeding months. ■

Can Regular Vigorous Exercise Become Addictive?

By Helen Ou

Regular vigorous exercise increases the secretion of a natural opium-like hormone, beta-endorphin, in the blood, according to a recent study. This hormone, released by the brain and pituitary gland, produces a sense of well-being and increases a tolerance to pain.

The study, conducted by Dr. Daniel B. Carr, Massachusetts General Hospital, and other researchers revealed that levels of beta-endorphin rose dramatically in the blood of non-athletes while exercising, and these levels increased even higher with regular training.

Seven female volunteers, 18 to 30 years old, who had not previously been exercising regularly, were placed on a two-month program of bicycling and running an hour a day to build up their levels of conditioning. Levels of beta-endorphin were measured in four sessions: a non-exercise control condition prior to entering the program, the first exercise session, an exercise session half-way through the program and the last exercise session (after two months of training).

Beta-endorphin levels increased substantially during each of the blood-measured exercise sessions as compared with the no-exercise control condition. Moreover, the amount of increase was significantly greater after a month of conditioning than at the beginning. After two months of conditioning, the increase after exercise was greater still, but not significantly greater than after one month.

The volunteers trained at 85 percent of their maximal heart rate during high intensity activity. The high intensity activity was increased from 20 minutes initially to 30, 40 and 45 minutes, respectively, and was maintained at 45 minutes for the final four weeks.

The increased beta-endorphin levels during exercise may explain "runners' high"—a condition similar to drug-induced euphoria. The effects of this hormone, though still speculative, could cause runners to become depressed when they miss a day of exercise, similar to withdrawal symptoms. The findings in this study are speculative, according to Carr, since hormone levels in the blood are being taken as an indication of what is happening in the brain, and in many ways, the brain is insulated from the blood. If these hormones accumulate in the brain, it could explain in part why people do not appear to notice injuries during strenuous exercise. However, many hormonal changes occur when people exercise and it is unlikely that these endorphins alone could explain the effects.

In addition, cumulative effects of repeated exercise appear to produce hormonal changes that may lead to altered reproductive function. More studies are necessary to find out how endorphins and other opiates inhibit pituitary gonadotropin secretion. The short and long term effects of exercise in women need further research to examine if they can cause delayed menstruation or result in amenorrhea (abnormal stoppage of menstruation). Earlier studies have shown that the relatively low fat content in women athletes inhibits menstruation.

Since the endorphins appear to induce a state of euphoria, thus possibly, reducing stress symptoms, continued study of this increase in hormone during exercise may lead to the development of new types of drugs for high blood pressure and such stress-related diseases as peptic ulcer, reproductive dysfunction and cardiovascular diseases.

According to Carr, the more scientists learn about the effects of exercise on the brain functions—in addition to the known effects on heart and muscles—the more they will be able to regulate it to get the best results.

This study was supported by grants from the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDK) and the Division of Research Resources (DRR) and was reported in the September 3, 1981 issue of *The New England Journal of Medicine.* ■

Joggers often have symptoms referred to as "runners' high" which appears to be attributable to increased secretion of hormones, known as beta-endorphins, in the blood.

NIH PHOTO 1728

Low Blood Pressure May Signal Nervous System Disorders

E [illegible]arilyn Sargent

New techniques for recognizing early signs of nervous system disorders are emerging from a series of NIMH studies on orthostatic hypotension, which is a lowering of blood pressure causing lightheadedness that may progress to loss of consciousness when standing up.

Dr. Irwin Kopin, Chief, NIMH Laboratory of Clinical Science, in a recent interview, explained that "when people stand up, baroreceptors in the cardiovascular system that are sensitive to changes in blood pressure send a message to the brain that says, 'blood pressure is going down and you had better increase it or this person is going to pass out.' This message is processed through the central nervous system and appropriate adjustments in blood pressure are made through mechanisms in the sympathetic nervous system. When this occurs, the neurotransmitter, norepinephrine, is released into the blood."

Studies of norepinephrine blood levels by Kopin and his colleagues differentiated two sets of orthostatic hypotensive patients, those with peripheral nerve loss and those with central nervous system damage.

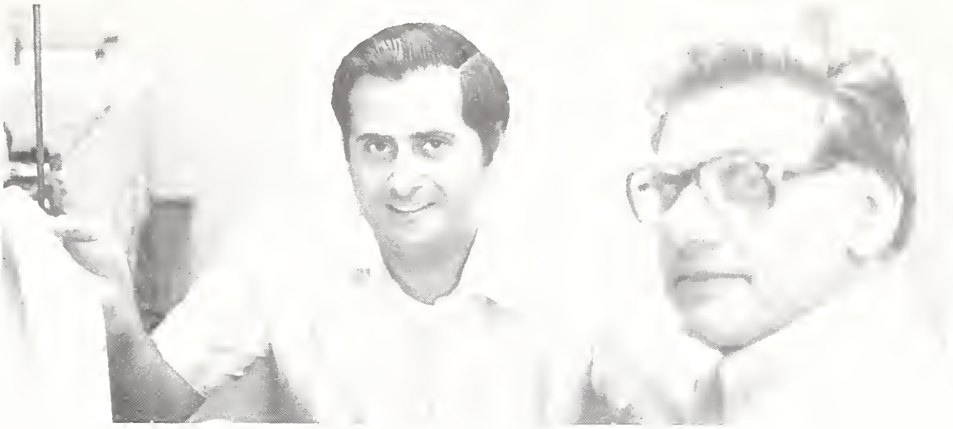
In cases of peripheral sympathetic nerve loss, the norepinephrine levels are abnormally low at all times, even when the individual is lying down. This indicates that the hormone is not being released in sufficient amounts at the nerve endings," Kopin reported.

"In the case of central nervous system involvement," he continued, norepinephrine levels are normal when the individual is lying down, but do not increase when he or she stands up, indicating that peripheral nerves are functioning but that the message is not being processed elsewhere in the system."

These findings confirm clinical observations in some patients of neurological abnormalities indicative of central nervous system disorders that are not evidenced in patients with peripheral nerve loss.

The norepinephrine research set in motion a series of other studies which have increased understanding of nervous system function, said Kopin.

For example, studies of blood sugar and norepinephrine levels following insulin-induced hypoglycemia (low blood sugar) in people with and without orthostatic hypotension have enhanced understanding of the adrenal medulla, an organ that secretes norepinephrine in response to hypotension and epinephrine (adrenalin) in response to hypoglycemia.



Dr. Irwin Kopin, Chief, NIMH Laboratory of Clinical Science, (right) works closely with Dr. Ronald Polinsky.

NIH PHOTO 1729

"When blood sugar goes down, you enlist the same sort of mechanisms to release epinephrine from the adrenal medulla as you do for releasing norepinephrine from the sympathetic nerve endings. We found that in normals, when blood sugar goes down following insulin, epinephrine levels jump up and return to normal as sugar levels rise," said Kopin, "but in some orthostatic hypotensive patients you do not see a similar jump in epinephrine after insulin reduces blood sugar because of deficient adrenal medullary responses."

"Nevertheless, other hormonal responses to hypoglycemia, such as those of glucogen, growth hormone, and cortisol are normal in these orthostatic hypotensive patients indicating that they are controlled by mechanisms different from those controlling glucose and norepinephrine," said Kopin.

In combination with the insulin research, the scientists also measured pancreatic polypeptide, a substance controlled by the vagus nerve, the main nerve of the parasympathetic system, said Dr. Ronald Polinsky one of Kopin's colleagues.

"We found that patients with orthostatic hypotension due to peripheral deficits did not have the normal increment of pancreatic polypeptide during hypoglycemia and very few patients with disordered central nervous system control had measurable increments, which is evidence that the parasympathetic system is also affected in these patients," Polinsky noted.

Pharmacological studies provided further clues to nervous system mechanisms and delineated a third group of patients, those who experienced tachycardia, increased heart rate, but not neurological symptoms in connection with the orthostatic hypotension.

These studies and comparisons of hormonal functioning in normal and orthostatic hypotensive patients have combined to give us the tools for early detection of organic dysfunction potentially important to diagnosing and treating mental and physical disorders, said Kopin.

Sexual impotence diagnosed as psychologically based, may in reality be the earliest symptom of orthostatic hypotension, a condition caused by nervous system dysfunction, says Dr. Kopin.

Kopin and his fellow researchers, who have been studying orthostatic hypotension, found that a number of their patients experienced impotence as the first sign of trouble. In some cases, said Kopin, the impotence showed up 5 to 10 years before the major sympton of orthostatic hypotension.

Because Kopin and his colleagues now have techniques for detecting possible underlying organic causes, they are interested in studying individuals diagnosed as psychogenically impotent.

"I believe we would find in many of these cases that the problem is organic and not psychological," said Kopin. "Although we do not have any cures or methods for preventing the possible development of such conditions as orthostatic hypotension, it may be useful to these men and their mates to know there is an organic problem. It could reduce a lot of anxiety and help them accept the condition."

Individuals who are interested in participating in such a study are invited to call Kopin at (301) 496-5082. ■

New Techniques and Drugs Improve Treatment of Heart Disease

By Susan Gerhold

Approximately 60 million Americans suffer from high blood pressure, 1.25 million people have heart attacks each year, and over 600,000 die from coronary heart disease and other heart complications annually. With statistics like these, heart disease and high blood pressure top the list of major chronic illnesses today.

Coronary heart disease was just one of the many topics discussed at the D.C. Medical Society meetings held last month in Washington, D.C. The two-day conference was jointly sponsored by the National Institutes of Health, and physicians from local hospitals and teaching universities from the area spoke on their specialities and latest medical findings.

Dr. Stephen Epstein, Chief, Cardiology Branch of the NIH's National Heart, Lung, and Blood Institute (NHLBI) predicted that recently developed techniques such as echocardiograms, radionuclide testing, and digital radiography will continue to aid the physician in diagnosing and treating vascular diseases before they become life-threatening to the patient.

In addition to these techniques, Epstein says that coronary artery bypass, percutaneous transluminal coronary angioplasty (PTCA), calcium and beta-blockers, all developed within the last decade or two, will continue to dominate the treatments for the 1980s.

The coronary artery bypass operation requires operating on the saphenous vein, a large vein removed from the leg, and then attached to the aorta, away from the area where the coronary vessels originate. The other end of the vein is connected to the coronary vessel below the obstruction, bypassing the diseased coronary artery. The procedure enables blood to flow once again to the area of the heart that was previously blocked by clogged or diseased arteries. Since the deficient area is bypassed, chest pain or angina, one of the first signs that continues to persist after a heart attack, diminishes.

The percutaneous transluminal coronary angioplasty (PTCA) was developed in the mid 1970s as an alternative to surgery. The patient is awake during the procedure which requires only three days of hospitalization. A catheter is inserted through the vein or artery to the heart and a balloon at the end of the catheter is inflated, opening the blocked passageway.

As the balloon inflates, it pushes arteriosclerotic plaque against the vessel wall, and enlarges the area so that blood can once again flow freely. Once this happens, the balloon is deflated and removed and the artery remains open. Physicians note that the patient no longer suffers chest pain and blood begins to flow to the heart at a markedly improved rate.

Calcium blockers, hailed as a major breakthrough in cardiotherapeutics, are used to treat abnormal heart rhythms, angina pain, and other heart problems. Calcium blocking agents such as verapamil, nifedipine, and diltiazem reduce the flow of calcium through the cell membranes of the heart and coronary vessels. Blood flows easier, improving the flow of oxygen to the organ and the heart doesn't have to work as hard to pump blood and oxygen back and forth.

Dr. William Friedewald, Associate Director, Clinical Applications and Preventive Program, Division of Heart and Vascular Disease, NHLBI, discussed drug therapy in the prevention of coronary heart disease. Of the three classes of drug therapy: lipid-lowering drugs (estrogen and clofibrate), platelet-active drugs (aspirin), and beta-blocking drugs (timolol, propranolol, atenolol), Friedewald said the beta-blocking drugs seem the most promising.

Beta-blockers work by blocking the action of a portion of the body's sympathetic nervous system. Currently they are used to treat angina pectoris; chest pains caused by clogged coronary arteries and high blood pressure. Within the last few weeks NHLBI investigators have released new clinical findings that indicate propranolol has shown to be most effective in treating patients who may be a higher risk than others in suffering from a second or third heart attack.

NHLBI unveiled the results of the double-blind study in which 31 medical centers throughout the country administered propranolol or a placebo to over 3,500 patients who had previously suffered heart attacks. The results of the clinical trial indicated that propranolol can reduce, by 26 percent, a patient's chances of dying within two years on the average after suffering a heart attack.

With such encouraging results, NHLBI discontinued the clinical trial 9 months early to encourage physicians to begin treating their high risk heart attack patients with propranolol immediate[illegible].

In addition to these new techniques, many physicians continue to urge their patients to modify their diets, to lower cholesterol levels and plan a daily exercise program to help aid in the fight against heart disease. ■

Two Eye-Institute-supported Researchers Win Nobel Prize

Prepared by the National Eye Institute
Information Office

Two long-time National Eye Institute grantees who began their research in a basement laboratory at Johns Hopkins University more than 20 years ago have won the 1981 Nobel Prize in Physiology or Medicine. Their prize-winning research has completely changed our view of how the brain processes signals sent to it from the eye and helped to place studies of the visual system in the forefront of brain research.

The NEI grantees, Dr. David Hubel and Dr. Torsten Wiesel, are now professors of neurobiology at Harvard University Medical School. They will share half of the $180,000 Nobel Prize; the other half will be awarded to Dr. Roger Sperry, of California.

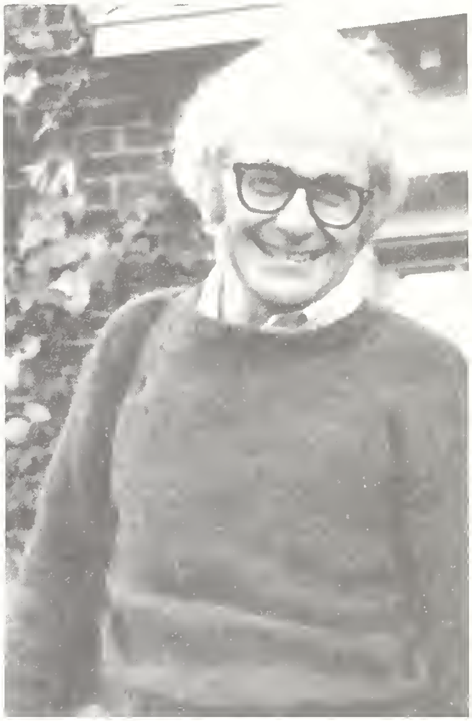
The Nobel Prize was awarded to the Harvard investigators for their demonstration of how the visual cortex of the brain processes information sent to it by the retina of the eye. The retina is the light-sensitive nerve tissue that lines the inside of the eye. The visual cortex is the [illegible] mantle of nerve cells that forms the [illegible] surface of the brain

The investigators discovered that among the millions of cells in the visual cortex, different types of cells relay different bits or features of an image. Certain cells, for example, are sensitive only to color or to size, others only to contrast, contour, movement, or spatial orientation.

These cells are organized into columns which represent increasingly complex stages in the visual process. Columns at the beginning of the process contain simpler cells than those at the later stages. Visual signals are transmitted through this hierarchy of cells in a carefully ordered manner. At the end of the process, the individual components are integrated into a single visual impression.

The process has been likened to syllable, word, and sentence construction. Certain brain cells pick up "letters" from the visual message that is received and then passed on by the retina. Other, more specialized cells construct "syllables" from the letters. The syllables are read in turn by higher level cells which turn them into "words," and then "sentences" are constructed by even more complex cell groups and sent to a higher center of the brain. There, the entire visual message, or image, is integrated and stored as memory.

NIH PHOTO 1730



NIH PHOTO 1731

Dr. David A. Hubel shared the Nobel Prize with Dr. Torsten N. Wiesel (left), both from Harvard.

Hubel's and Wiesel's elucidation of this visual process revealed that, seeing is an astonishingly complex process. Until then, scientists knew that seeing actually takes place in the brain, but the process was assumed to be much less complicated, a simple point by point transfer of the visual image on the retina to an image projected onto the cortex of the brain.

In addition to shedding light on how the brain processes visual information, Hubel and Wiesel also found that visual cells require normal visual stimulation in infancy if they are to function properly later in life. If a newborn has an eye disorder which distorts the image received or obscures it at this critical stage of development of the visual cells, the ability of these cells to pick up, transmit, and analyze visual impressions may be forever impaired.

Congenital cataract is an example of a disorder which can cause profound changes in cells by depriving them of normal visual stimulation at a critical period in infancy. A cataract is a cloudy or opaque area in the natural lens of the eye which interferes with the passage of light to the retina, thereby impairing vision. Congenital cataract—which affects babies and children—may obscure sight, thereby partially or completely depriving an infanct of normal visual stimulation.

These findings already have influenced treatment of cataract and other blinding or vision-distorting conditions in children. Congenital cataracts now are removed within two months after birth instead of at six to 24 months. Strabismus (crossed eyes) and amblyopia (lazy eye) also are corrected as early as possible in an effort to prevent or reduce the amount of permanent visual impairment. If the sight in one eye is obscured and distorted, the actual proportion of brain cells capable of responding to signals from that eye decreases and eventually it becomes impossible for that eye to see.

Drs. Hubel and Wiesel continue to pursue research on the visual system with support from the NEI. Dr. Hubel's FY 1981 research grant is for $167,308 in direct costs. Dr. Wiesel is currently receiving $392,178 in direct costs, for two research grants, a training grant, and support for a research core facility. ■

Therapy for Soft Tissue Sarcoma Improves Survival

Prepared by the Office of Cancer Communications

Researchers at the National Cancer Institute (NCI) have announced a major advance in treatment of patients with soft tissue (muscle, fat, nerve, and connective tissues) sarcoma of the extremities. Carefully designed combination treatments—surgery, radiation, and chemotherapy—have dramatically increased survival rates and spared the majority of these patients from amputation of a limb, the researchers reported.

"Our studies reinforce the fact that careful application of the right combination sequences, and amounts of treatment can produce substantial improvement in patient outcome," Dr. Steven A. Rosenberg, Chief, NCI Surgery Branch, and principal investigator, commented. "A major finding of the studies is that aggressive use of chemotherapy immediately after surgery can lead to marked improvement in freedom from disease recurrence, and possible cure of these patients. The chemotherapy was given even though there was no clinical evidence of disease spread at that time."

In two recent NCI studies, the disease-free, three-year survival rates of patients in the treatment groups rose to 91 percent compared to generally reported 40 to 50 percent survival rates in such patients. Most recurrences are known to take place in the first two years after therapy. A total of 107 patients were involved in the studies.

"While long-term followup of patients in the NCI studies will be needed," Dr. Rosenberg added, "this effective treatment of other soft tissue sarcomas uses principles that may be applicable to the treatment of other solid tumors with low cure rates."

The new treatment strategies developed at NCI for soft tissue sarcomas of the extremities have not only increased survival rates, but substantially improved the quality of life. Limb sparing was possible in most of the patients without additional risk of disease recurrence.

The researchers also made special efforts to define and monitor side effects of radiation and chemotherapy with the ultimate goal of minimizing toxicities associated with effective treatments.

Soft tissue sarcomas are cancers of the connective tissue, such as muscle, fat, and nerves. These sarcomas are highly malignant solid tumors which strike mostly people in their 20's, 30's, and 40's. There are an estimated 5,000 new cases a year in the U.S.

Most soft tissue sarcomas occur in the extremities and local recurrence rates following standard treatment (limited excision or amputation) outside of NCI studies have been about 40 percent. The tumors tend not only to recur locally but tend to spread early to the lungs. The challenge is to develop treatments to prevent both while preserving the limb.

The NCI studies were designed to determine optimum use of surgery and radiation for "local" control, and chemotherapy for "systemic" control (spread of tumor to other areas). Chemotherapy may also enhance local disease control. The goal was to increase patient survival and to see if less radical procedures combined with other treatments could safely preserve functional limbs.

The NCI studies of patients with soft tissue sarcoma of the extremities were conducted by the Surgery Branch, in conjunction with the Radiation Oncology and Medicine Branches. Results of the studies were presented in a report to the Division of Cancer Treatment Board of Scientific Counselors, October 1, at NCI.

Researchers collaborating with Dr. Rosenberg in the recent studies are: Dr. Eli Glatstein and Dr. Joel Tepper, Radiation Oncology Branch; and senior surgeons, Surgery Branch, NCI. Currently, NCI has expanded these studies and is now accruing patients for clinical trials to maintain effective treatment while minimizing associated toxicities. ■

Rare Form of Cancer in Homosexual Men Stimulates Research

By Mary Donovan

The sudden occurrence of a rare form of cancer in homosexual men has brought together researchers interested in studying the myriad of variables involved in the development of cancer. The uncommon, yet prototypic form of cancer, known as Kaposi's sarcoma, was the focus of a recent workshop sponsored by the National Cancer Institute in conjunction with the Centers for Disease Control.

Originally described in 1872 by a Hungarian dermatologist, Kaposi's sarcoma is a type of skin cancer primarily seen in older men of Jewish and Italian descent. In 1979 it was diagnosed in 11 homosexual men, quite by accident, when researchers were treating these patients for another disease. Since then, 55 more cases have been found, and according to Dr. James Curran of the Centers for Disease Control, Kaposi's sarcoma "may be a new public health problem."

Investigators are puzzled at the prevalence of this disorder in homosexuals, leading them to question the role that lifestyle plays in cancer. Many of the Kaposi's patients have had multiple sex partners and almost all at one time have used inhalants, such as smelling salts. Some also have a history of venereal disease. Detailed clinical and personal profiles will assist researchers in identifying more closely the relationship between these factors and the disease. The sudden onset and association with homosexuals suggest that prevention may be possible by eliminating the risk factors or variables connected with the disease.

In the initial stages, small brownish-purplish patches appear on the skin, often resembling mosquito bites and moles. These are followed by tumors that develop internally, attacking the gastrointestinal tract, liver and lungs. Each tumor appears to arise individually rather than as a metastases or spread. In the older patients, the disease may linger on for twelve to fifteen years, whereas the younger untreated victims survive only a few years at most.

Kaposi's sarcoma has also been observed in young black men, women and children living in Equatorial Africa. The progress of the disease in these individuals and in the homosexual men appears to be similar. No other apparent connection between the two groups has been recognized. Researchers believe that studying the epidemiology of Kaposi's sarc[illegible] will lead them to more clues about the cause.

Indirect serologic information strongly suggests an association with an infectious agent, most probably a virus. Some scientists speculate that the suspected virus grows in the gastrointestinal tract and is spread by sexual contact. In some studies, for instance, evidence for the presence of cytomegalovirus (CMV) has been found in the blood of Kaposi patients, but conclusive proof is not available. At present only a few human cancers are thought to be caused by a virus.

Like the chicken and the egg question, scientists don't know which came first when it comes to the marked immunosuppression observed almost universally in these patients. Multiple factors are probably involved, such as the use of recreational drugs, poor nutrition, a history of recurrent infections and possible genetic factors. From animal studies, certain viral infections have been shown to depress the immune system and may well be the mechanism at work in man. One added complication to this theory is that the degree of immunosuppression in Kaposi's victims is extreme compared with that observed in "normal" CMV patients.

Kaposi's sarcoma appears to respond to certain types of chemotherapy, and, in some cases, to radiation therapy. Still, the prognosis is not always hopeful for its younger victims. More research, according to the workshop participants is needed to improve present methods of treatment and to explore new ones, such as immunotherapy, which may eventually prove to be more promising.

In addition, a large-scale surveillance study is about to begin to determine the extent of the disease and to identify differences between the homosexual men who develop Kaposi's sarcoma and those who don't.

Researchers are also exploring more closely the relationship between the development of the disease and the suppression of the immune system, in addition to furthering efforts to identify the causative agent. Much of this work involves collecting blood and biopsy samples that are analyzed and compared with control groups.

A comprehensive clinical study is being developed by NCI staff and a committee of investigators from the following institutions: the Centers for Disease Control, the University of California at San Francisco, New York University Medical Center, Sloan-Kettering Memorial Hospital and the University of Miami.

As Dr. Bruce Chabner, Acting Director, Division of Cancer Treatment, NCI, reminded the attendees, "Kaposi's sarcoma is an accident of nature that has potential for greatly furthering our understanding of the cancerous process if studied by a variety of approaches." ■

Study Finds Promise in Male Contraceptive Hormone

By Maureen Gardner

Scientists working to develop a male birth control drug have reported promising findings after tests on a powerful synthetic brain hormone called LHRH-A.

In a recent study on eight men at Vanderbilt University in Nashville, LHRH-A proved it can suppress sperm production. However, it also lowered the sex drive and produced other unwanted effects that disappeared once treatment was stopped. Researchers are now studying ways to avoid these problems and yet retain the hormone's contraceptive effects.

In the September 17 *New England Journal of Medicine*, which published the study results, an editorial heralded the Vanderbilt work as "an exciting beginning in the exploration of the contraceptive potential" of LHRH-A in men.

LHRH-A is a man-made modified version of natural LHRH (luteinizing hormone-releasing hormone), a hormone that plays a major role in the control of reproductive events. Natural LHRH is released in the brain and stimulates the pituitary gland just beneath it.

LHRH causes the pituitary gland to secrete hormones called gonadotropins which are carried through the bloodstream to the testes in men and the ovaries in women. In men, the gonadotropins promote the production of sperm and the male sex hormones, including testosterone—itself a key hormone needed for sperm production. Thus, natural LHRH is essential to normal fertility.

Although LHRH-A is more than 100 times as potent as natural LHRH, it does not simply intensify natural LHRH's fertility-promoting effects, as might be expected. Depending on the dosage and timing of administration, LHRH-A acts as an anti-fertility agent. This is known as a "paradoxical inhibitory" effect.

The Vanderbilt study, supported in part by NICHD, showed for the first time that LHRH-A can have this paradoxical inhibitory effect in human males. Eight volunteers injected themselves with LHRH-A daily, following instructions by the researchers. The amount of testosterone in the blood fell, as did sperm production; the drug also reduced the sperm's ability to move. The low testosterone levels caused problems: reduced sex drive, impotence, and even "hot flashes" similar to those experienced by women after menopause. All of the subjects recovered within 14 weeks after treatment was stopped.

Scientists think that the repeated low doses of LHRH-A may have caused the pituitary gland to give weakened signals to the testes for the production of sperm and sex hormones. However, the investigators are not discounting the possibility that LHRH-A acted directly on the testes.

Researchers are now trying to harness LHRH-A's effects. A possible solution is to combine LHRH-A with testosterone. However, this idea raises questions about whether added testosterone can forestall the side effects without restoring sperm production.

Despite problems that must be overcome, scientists believe that LHRH-A shows promise as a male contraceptive of the future. Because LHRH-A breaks down quickly in the body, it is expected to be safer than currently available hormonal contraceptives.

It is difficult to predict the final form LHRH-A will take. "With certainty, daily injections are not considered the final form," according to Dr. Gabriel Bialy, Chief of NICHD's Contraceptive Development Branch. Dr. Bialy notes that daily injections, though essential for life-threatening conditions such as diabetes mellitus are not practical for contraception.

Several alternate routes are under consideration. In other countries, LHRH-A is being tested in men and women as a contraceptive nasal spray, and U.S. trials are forthcoming. Through the nasal passages, the hormone is readily absorbed into the bloodstream. A problem with this method is that nasal congestion from colds or allergies could hinder the absorption of the hormone.

LHRH-A is readily absorbed through the lining of the vagina, so in women this may be an alternate route of administration. Dr. Bialy believes that with time, and with advances in hormone synthesis or formulation, a form of LHRH-A that can be absorbed under the tongue may be feasible. ■

"ACRF" Glass Tower Dedicated in October

By Susan Gerhold

On October 22, 1981, the 13-floor glass structure popularly called the "ACRF" was dedicated as the Warren Grant Magnuson Clinical Center of the National Institutes of Health. The ACRF or Ambulatory Care Research Facility will provide thousands of outpatients ambulatory care in a research setting.

The existing all-brick 14 story building will continue to house over 7,500 inpatients each year and offer the same excellent care that patients have been receiving since the Clinical Center first opened its doors over 28 years ago.

This new addition, with its glass tower, skylights, open waiting rooms, large amphitheater, operating rooms, and clinics will serve over 200,000 patients each year. The design of this building will continue to carry the idea of scientists working at the bench in close proximity with the patients on the floors. Clinics will be located near the research areas, and through a walkway in-house patients and researchers will still be close by.

Senator Magnuson, after whom the building was named, has been a champion fighter for promoting the continuing programs in health care and research. He was called the "Commander in Chief" of the war against cancer and heart disease. He was the chairman of the Subcommittee on Labor-HEW of the Senate Committee on Appropriations, which had full jurisdiction over the NIH. In 1978 he became the chairman of the full committee. Without the Senator's constant leadership and backing, there would be no National Cancer Institute, a proposal Magnuson introduced in 1937. His unwavering commitment to the idea that the conquest and prevention of disease, as well as progress in health care depended upon research is noted in a plaque that will greet visitors as they enter the new building.

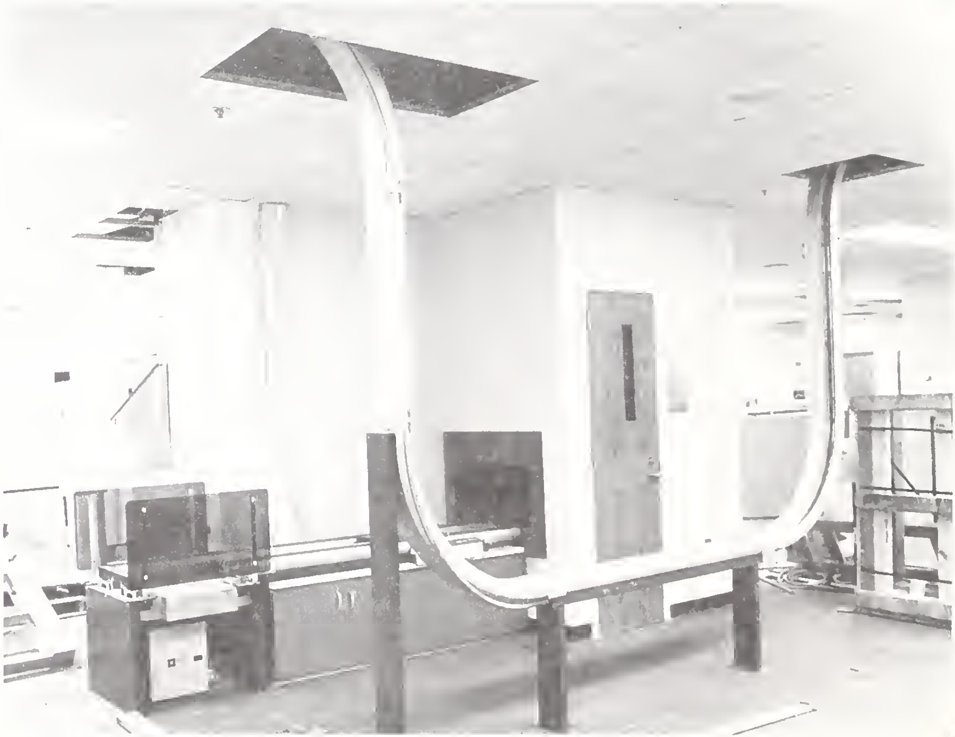
Construction began for the ACRF in June 1977 as part of the modernization and expansion program designed to strengthen the combined laboratory and patient care activities. The new facility will provide care for more than double the current outpatients seen in clinics each year and at the same time provide for the expansion of laboratory research to support the outpatient clinic program. The ACRF will allow for many more non-invasive procedures to be performed on an ambulatory or out-patient basis instead of keeping patients hospitalized as done in the past.

The new lobby, admissions area, cafeteria, and visitors center will give the appearance of an open and breezy area way so that hospital patients, their families and our staff can look out on any of the three levels shown here and see what's going on—on the floors below or above. NIH PHOTO 1732

The building will have three underground floors for parking, and corrido will connect each floor in the new glass tower to the corresponding floor in the main building.

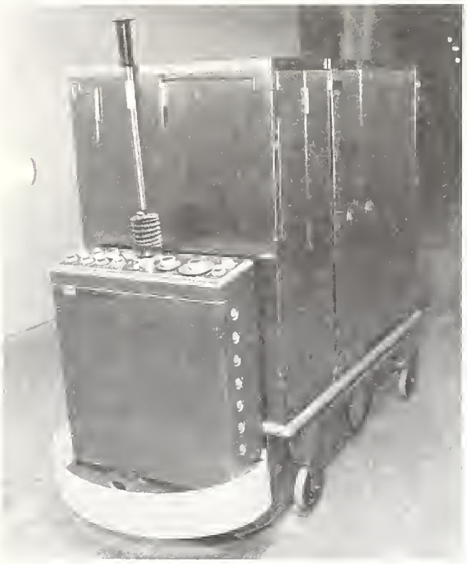
The open-spaced lobby complete with skylights and plants will serve as the NIH Visitors Center and exhibit area, museum, theater, and model laboratory. The first floor will staff an admissions section, for out-patients to check in and report to the clinics. The Diagnostic Radiology and Nuclear Medicine Departments, currently located in existing Building 10, will move to the ACRF this spring, and will also be located on the first floor. In addition, there will be another cafeteria on the second floor for staff, outpatients and their guests. Also, on this floor is the Clinical Pathology Department which is designed to accommodate 200 people divided into four sections: Hematology, Immunology, Chemistry, and Microbiology.

Floors 3 to 13 are designed alike. Each floor will have clinic rooms on the west side and laboratories on the east side, and isolated animal areas will be located in the southeast corner of each floor. All floors will be served by three patient elevators located at the north side of the tower, and three elevators for staff will be located at the south side of the building. Walkways on each floor will give easy access to Building 10's existing Clinical Center.



This section is located within Clinical Pathology. Tote boxes will run along a track throughout the hospital, carrying specimens, blood, and supplies to Clinical Pathology and other departments.

NIH PHOTO 1733



There are 28 new "robots" that will wander around the ACRF next year. They are fully automated, and will be used to deliver supplies to the new clinics and offices throughout the building.

NIH PHOTO 1734

Through the lobby's skylight the glass tower is visible. The glass tower is thirteen stories high and will house outpatient facilities, waiting rooms, operating rooms, play areas for the smaller outpatients, and a cafeteria.

NIH PHOTO 1735

The new Clinical Pathology quarters are almost the size of a large football field. The "doggie-bone" laboratory areas will house 200 employees from the four sections of the Department.

NIH PHOTO 1736

Each clinic will have a nursing station or check-in area for patients to sign in and then wait for their appointments in the waiting rooms adjacent to the check-in area.

NIH PHOTO 1737

Exotic Viral Infection Gives Clues About Other Diseases

By Maureen Miller, student intern for the NIH News Branch

Kuru, a rare and exotic viral infection which afflicts the Fore natives of New Guinea has been for many years a major project of Dr. Carleton Gajdusek, Chief, Central Nervous Systems Studies, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The disease, which Gajdusek brought to the attention of the medical world in 1957, leaves it victims with uncontrollable tremors similar to Parkinson's disease. Gajdusek and his colleagues have subsequently found that the disorder is caused by a slow virus which enters the victim's body early in life and remains latent from 5 to 40 years before causing a rapidly progressive illness that leads to death within a year.

Gajdusek's team has spent several years studying this degenerative disease that was the primary cause of death among the Fore people. They found that the virus destroyed the brain without signs of inflammation or stimulation from the body's immune system, and also noted that the virus continued to live in the victim's body without symptoms until advanced stages of disease—years later.

As they discovered more about the disease, the team found that the virus was quite atypical, that it did not have a core, has no non-host protein in its structure, and that its nucleic acid could not be demonstrated by conventional techniques. They also found that kuru had no host other than man, no disease carrier channels, and no apparent source in nature. "Man," Gajdusek said, "was the only source for spreading the virus."

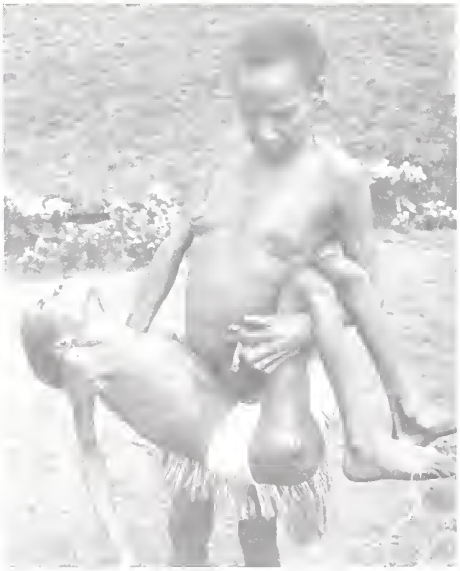
Later Gajdusek and his colleagues connected kuru with the Fore tribes ceremony to the dead: endocannibalism. "The artificial and only source of contamination was by a ritual in which, out of respect for the dead, the Fore people consumed the brain and all the tissues of their close, dead relatives," said Gajdusek. He also found that women and children participating in the ceremony suffered infections in their nasal passages, skin and mouths.

After the first 20 years of his studies, Gajdusek's team was able to confirm retrospectively that 95 percent of all female deaths among the Fore tribe was due to Kuru. This high mortality rate was partially offset by a high rate of fertility. In their attempts to keep abreast of kuru, the Fore customarily arranged pre-pubertal marriages and promoted early childbearing practices for the young brides. However, this custom could not keep up with the deadly virus, and Gajdusek noted that only two out of every six infants survived to puberty.

Gajdusek's research on kuru provided a valuable source of knowledge for another disease called Creutzfeldt-Jakob disease. This disease is also rare, but is widely distributed throughout the world. Researchers have noted the disease seems to be familial in 10-20 percent of cases, and have also noted that the infection may

Dr. Carlton Gajdusek received the Nobel Prize in physiology and medicine in 1976 based on his pioneer efforts in the field of slow viruses.

NIH PHOTO 1738



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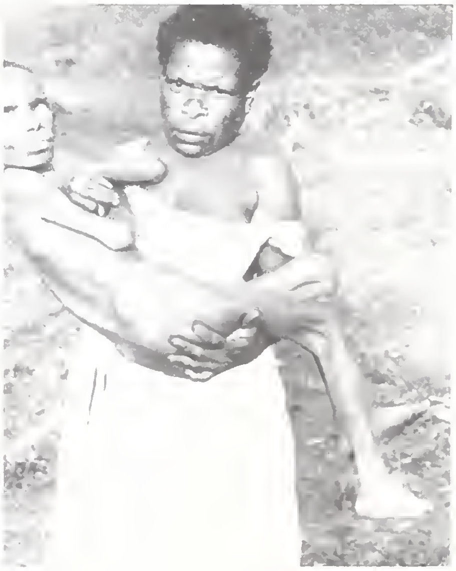

NIH PHOTO 1740

Fore parents continue to care for their stricken young and try to keep abreast of the virus by promoting young marriages and more children.

appear in the first years of the victim's life, similar to kuru, but later causes disease when the victim reaches age 40 or older.

The infection may be spread by surgical instruments contaminated by the virus. In this instance, patients undergoing surgery or other medical reasons, are infected with the virus unknowingly as the surgeon implants the virus directly into the body from a previous patient who has been infected.

After realizing that surgical instruments could spread the disease, physicians all over the world began to revise operating procedures to eliminate contamination by autoclaving all surgical instruments.

In summary, Gajdusek noted that the exotic, isolated population of the Fore has enabled the scientific community to acquire a better understanding of Creutzfeldt-Jakob disease and of the nature of slow viruses in general. Physicians now know how to eliminate the surgical spread of Creutzfeldt-Jakob disease. Gajdusek now focuses attention on the question of whether Creutzfeldt-Jakob patients have been blood donors, and worries about other sources of iatrogenic contamination, such as might be taking place when youngsters visit the dentist or undergo blood transfusions. Will a small unlucky child thus be doomed to a life of civilized world kuru? ■

Dr. Gajdusek gathered medical information from the new Hebrides Tribe in 1972.

NIH PHOTO 1741

Dr. Gajdusek, (center) several years ago with Fore youngsters.

NIH PHOTO 1742

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Ms. Maureen Napper
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